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LIPOID NEPHROSIS

A STUDY OF NINE PATIENTS, WITH SPECIAL REFERENCE TO THOSE OBSERVED OVER A LONG PERIOD

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A problem of fundamental importance in the clinical study of any form of Bright's disease is a consideration of the length of time the patient has been observed. This is particularly true in the study of lipoid nephrosis because a diagnosis cannot be made with any degree of certainty without a long period of observation. Too often a patient is studied during one stage of the disease, and the signs and symptoms observed in this brief period are considered to constitute the true picture of the renal disorder. In chronic glomerulonephritis the variability of the clinical features often leads to confusion in their proper interpretation. At one time all the major symptoms—albuminuria, edema, hypertension, nitrogen retention and occasionally a convulsion—may be present. Later, hypertension and nitrogen retention may disappear, and albuminuria and edema may be so pronounced that lipoid nephrosis is thought to exist. At another stage of the disease there may be no edema, but hypertension, hematuria and retinopathy may furnish sufficient evidence for a diagnosis of chronic glomerulonephritis.

One of the main obstacles to the proper identification of lipoid nephrosis has been the failure to study patients carefully over a long period. Most cases that are loosely called cases of lipoid nephrosis are examples of chronic glomerulonephritis with extensive lipoid degeneration of the tubules. Even in some published reports it is seen that

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the blood pressure later rose and genuine uremia developed. In our opinion these were not cases in which lipoid nephrosis developed into chronic glomerulonephritis but were cases of chronic nephritis from the beginning. The confusion that has existed because chronic glomerulonephritis may be characterized by edema is beginning to disappear. Observations have convinced us that in the course of chronic nephritis there may be periods lasting from weeks to months in which the nephrotic syndrome dominates, yet further study proves conclusively that the case is one of chronic glomerulonephritis with secondary lipoid nephrosis.

In an attempt to draw a line of differentiation between the apparently degenerative and the evidently inflammatory renal lesions, Mueller,[1] in 1905, proposed the term nephrosis for the primary degenerative diseases. This distinction was not accepted without considerable criticism, especially from such German pathologists as Löhlein[2] and Aschoff,[3] but later this term was popularized by Munk[4] and Volhard and Fahr.[5] The nephroses, according to Munk's classification, include several types of degeneration of the renal tubules. For example, there are (*a*) albuminous degeneration, (*b*) fatty degeneration, (*c*) hyaline degeneration, (*d*) amyloid degeneration, (*e*) glycogen degeneration, as seen in diabetes mellitus, and (*f*) lipoid nephrosis. It is the type called lipoid nephrosis by Munk, genuine nephrosis by Volhard and Fahr[5] and chronic nephrosis by Epstein[6] that is the problem for discussion here. Clinicians, particularly Christian,[7] of this country, and Gainsborough,[8] of England, and pathologists, notably Bell[9] and Shaw Dunn,[10] have refused to accept the condition as anything more than a phase of glomerulonephritis. Recent work, especially that by Randerath[11] and

1. Mueller, F.: Morbis Brightii, Verhandl. d. deutsch. path. Gesellsch. **9**:64, 1905.

2. Löhlein, M.: Ueber Fettinfiltration und fettige Degeneration der Niere des Menschen, Virchows Arch. f. path. Anat. **180**:1, 1905.

3. Aschoff, L.: Ueber den Begriff der "Nephrosen" und "Sclerosen," Deutsche med. Wchnschr. **43**:1345, 1917.

4. Munk, F.: Die Nephrosen, Med. Klin. **12**:1019, 1916.

5. Volhard, F., and Fahr, T.: Die Brightsche Nierenkrankheit: Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

6. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis: Method for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.

7. Christian, H. A.: Nephrosis: A Critique, J. A. M. A. **93**:23 (July 6) 1929.

8. Gainsborough, H.: Study of So-Called Lipoid Nephrosis, Quart. J. Med. **23**:101, 1929.

9. Bell, E. T.: Lipoid Nephrosis, Am. J. Path. **5**:587, 1929.

10. Dunn, J. S.: Nephrosis or Nephritis? J. Path. & Bact. **39**:1, 1934.

11. Randerath, E.: Die Entwicklung der Lehre von der Nephosen in der pathologischen Anatomie, Ergebn. d. allg. Path. u. path. Anat. **32**:91, 1937.

Fahr,[12] has exemplified the changing conception of the relation between the two diseases. The idea is growing that lipoid nephrosis is distinct and that hyperpermeability of the glomerular capillaries without demonstrable damage to the capillary walls leads to the morphologic changes seen in the tubular epithelium and glomeruli. If the confusion that has arisen between lipoid nephrosis and other forms of Bright's disease is to be overcome, it is essential to identify its characteristic features by prolonged observations and with great precision.

Our purpose in reporting this series of cases is to show by extended clinical study and histologic examination that lipoid nephrosis is essentially distinct from chronic glomerulonephritis with the nephrotic syndrome and that there is justification on clinical grounds alone for retaining the term. Apart from the argument over the identity of lipoid nephrosis, it is thought that to establish it as an entity may arouse more active investigation into the cause of the hyperpermeability of the glomeruli for albumin, the production of edema and the abnormal metabolism of cholesterol. However, it is not our aim to solve the problem of the functional changes around which the excessive albuminuria and edema revolve. A clinical study of the 9 cases presented here, with a careful and prolonged follow-up study of some of them and an examination of the histologic changes in others, may help to clarify some aspects of the controversy.

The histologic examination of the kidney in so-called lipoid nephrosis shows how the confusion has arisen. Frequently there has been a lack of correspondence between the clinical and the pathologic features, and at autopsy patients with supposed lipoid nephrosis have been found to have chronic glomerulonephritis. In such instances the period of clinical study has usually been too short for a correct diagnosis. Often when the kidney fails to show the classic histologic picture of chronic glomerulonephritis, special stains reveal minimal glomerular changes. These are considered by some to be inflammatory changes and by others degenerative. However, this difference of opinion does not lessen the importance of the fundamental fact that patients with such renal changes have a course that is very different from that of patients with true glomerulonephritis.

The clinical and histologic features of lipoid nephrosis have recently been surveyed so comprehensively by Leiter[13] that further amplification is hardly necessary now. Furthermore, two of us[14] (Drs. Murphy

12. Fahr, T., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1934, vol. 6, pt. 2, p. 829.

13. Leiter, L.: Nephrosis, Medicine **10**:135, 1931.

14. Murphy, F. D., and Warfield, L. M.: Lipoid Nephrosis, Arch. Int. Med. **38**:449 (Oct.) 1926.

and Warfield) have discussed the disease fully in a previous report. In brief, it is identified clinically by both positive and negative features. There are marked albuminuria, hypercholesteremia, edema and doubly refractive lipoids in the urine, but just as important are the lack of hypertension, nitrogen retention and genuine uremia and the freedom from an abnormal number of red blood cells in the urinary sediment. Any indications of cardiovascular changes, such as cardiac hypertrophy, arteriosclerosis or albuminuric retinitis, are conspicuously absent. Reduction of the plasma protein content, particularly a deficit of plasma albumin caused by the marked albuminuria, has come to be looked on as an important clinical feature. The course of lipoid nephrosis extends over a period of months to several years and frequently terminates in complete recovery. Occasionally during the periods of extreme edema a secondary infection, often pneumococcic, develops and causes pneumonia or pneumococcic peritonitis.

REPORT OF CASES

In this report 9 cases which fulfil the rigid requirements for a diagnosis of genuine lipoid nephrosis are discussed. Cases 1 to 3 were reported in an article published in 1926.[14] Two patients (cases 2 and 3) have been observed periodically since that time, and an after-study is given here. Two of the 9 patients died and were studied post mortem, 6 recovered completely and 1 is under observation at present.

CASE 1.—A man aged 21 entered the hospital on Oct. 27, 1924, complaining of headache and swelling of the legs. The past history was unimportant except for scarlet fever at the age of 10 and gonorrhea at 20.

Physical examination revealed a well built, well nourished, pale man with considerable edema of the legs, face and eyelids. The lungs, heart, abdomen and eyegrounds were normal. There was no dyspnea. The blood pressure was 118 systolic and 70 diastolic, and the blood vessels were soft. The reflexes were normal.

Urinalysis showed considerable albumin, no red blood cells, a few leukocytes, hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed 500 mg. of cholesterol per hundred cubic centimeters. The serum looked milky. The Wassermann reaction was negative. The phenolsulfonphthalein test showed 60 per cent excretion in one hour. The blood count was normal. The basal metabolic rate ranged between —10 and —15 per cent.

While the patient was under observation in the hospital the edema fluctuated, reaching a degree so severe at times that the skin cracked; during such periods he became semicomatose. These fluctuations apparently had no relation to treatment, although large doses of thyroid seemed to prolong the interval between attacks. During the attacks the urea nitrogen and the creatinine content of the blood remained normal, but the cholesterol content rose. The albuminuria remained marked at all times. The patient died eighteen months after admission to the hospital. Partial necropsy was performed.

Gross Postmortem Description.—There was a small amount of clear, yellow fluid in the peritoneal cavity, and the tissues were slightly edematous. The

kidneys were large, firm and pale. The capsule stripped with ease, leaving a smooth, pale surface which was mottled creamy white and pink. The cortex was a creamy white and was greasy in appearance. It measured 12 to 14 mm. in thickness and was well marked off from the pyramids. The pelves appeared normal.

Microscopic Postmortem Description.—The glomeruli showed no signs of inflammatory change. The proximal convoluted tubules revealed extensive and profound degenerative changes. The cells were pale and swollen, and the nuclei were often not visible. The protoplasm looked granular, and the lumens of the tubules were filled with granular débris. There were doubly refractive lipoids in the tubular epithelial cells. The collecting tubules and small arteries showed no definite changes. The adrenal glands, spleen, liver and heart were normal in appearance. On section the liver was pale, edematous and moderately congested. The heart showed a slightly raised, yellowish area in the aortic leaflet of the mitral valve. The abdominal aorta showed numerous yellowish, elongated areas slightly raised above the surface, as well as small rounded, button-like areas. Sections of the aorta through one of the yellow patches showed characteristic lesions of atheroma in the intima. Many refractive lipoids were present.

CASE 2.—A woman aged 25, a stenographer, began to have headaches and puffiness of the face and ankles in 1921. Urinalysis at that time showed marked albuminuria, a few white blood cells, an occasional cast but no red blood cells.

In 1922 a more complete examination was made. The heart and lungs were normal. The edema, which had come and gone during the last year and a half, was marked. The blood pressure was 122 systolic and 84 diastolic. The Wassermann reaction of the blood was negative. The blood counts were normal. Renal function tests revealed no insufficiency.

During 1923 and 1924 the edema and headaches fluctuated, and the quantity of albumin in the urine varied considerably. The blood pressure remained normal. During this time the patient continued to work.

Urinalysis on Dec. 5, 1925, showed 2 plus albumin, a specific gravity of 1.024, no red blood cells, a few pus cells and many doubly refractive lipoids. Chemical examination of the blood showed nonprotein nitrogen, normal, and cholesterol, 384 mg. per hundred cubic centimeters. Various diets and treatments, including the use of thyroid, were given, but no therapeutic agent seemed to have much influence.

This patient has been under observation from time to time until the present. Since 1925 there has been no edema. The albuminuria subsided, and there has been no recurrence. She is working regularly and appears to have recovered completely from the lipoid nephrosis.

CASE 3.—A man aged 24 entered the hospital on Dec. 9, 1925, complaining of swelling of the ankles and face, headache and loss of appetite. The symptoms developed two months before entry without apparent cause. They subsided after some treatment but returned. The past history was unimportant except that he had gonorrhea at the age of 18.

Physical examination revealed considerable edema of the legs and face. The heart, lungs and liver were normal. The blood pressure was 125 systolic and 75 diastolic. The Wassermann reaction was negative. The eyegrounds were normal.

Urinalysis showed 4 plus albumin, no red blood cells and many doubly refractive lipoids. Chemical examination of the blood showed 666.6 mg. of cholesterol per hundred cubic centimeters. The basal metabolic rate averaged + 10 per cent.

The edema fluctuated in intensity and at times became so pronounced that the patient was confined to bed for a number of weeks. The marked albuminuria persisted. After March 1, 1926, the edema disappeared entirely and never returned. For a number of months there was moderate albuminuria, which gradually diminished until about April 1927, when only a trace of albumin was found in the urine. He was reexamined in 1931 for the purpose of presentation at a clinic and was apparently perfectly normal at that time. In May 1937 he was examined again and, as the chart shows, was found to be normal in every respect.

CASE 4.—A woman aged 32, entered the hospital on Jan. 24, 1925, for the treatment of generalized anasarca. The past history was unimportant except for diphtheria at the age of 8 years and the infections of the upper respiratory tract that are common in childhood. The present symptom came on slowly and painlessly without apparent cause in September 1924. The edema was intermittent for several months. There were no other complaints.

Physical examination at the time of the patient's entrance into the hospital revealed pronounced generalized anasarca. The heart was normal, and the blood pressure was 130 systolic and 80 diastolic.

Urinalysis showed 4 plus albumin, a specific gravity of 1.017, an occasional red blood cell, 2 or 3 pus cells, 2 to 4 hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed nonprotein nitrogen, 26.6 mg.; urea nitrogen, 11.1 mg.; creatinine, 2.2 mg., and cholesterol, 490 mg., per hundred cubic centimeters. Renal function tests showed: phenolsulfonphthalein, 50 per cent excreted in the first hour and 25 per cent in the second; dilution and concentration, 1 to 1.022.

The edema fluctuated during the spring of 1925, and in May it disappeared entirely. The albuminuria persisted during 1926 and 1927, but there was no further recurrence of edema. The patient was last seen on Aug. 10, 1934. At that time she was perfectly normal except that there was a trace of albumin in the urine.

CASE 5.—A man aged 18, a truck driver, entered the hospital on July 25, 1930. He complained of edema and oliguria which had lasted for twelve weeks. He had been in good health before that time. The swelling began in the face and spread over the entire body. Some pain and dyspnea were associated with it.

The patient had had mumps, measles, influenza and gonorrhea. The family history was unimportant.

Physical examination revealed a well developed, pale, pasty-looking boy who was so edematous that he lay on his back and had difficulty in moving. The pharynx was injected, and the tonsils were enlarged. The lungs and the heart were normal. The blood pressure was 112 systolic and 70 diastolic. There were draining perforations and many bullae in the right lower portion of the abdomen. The extremities were greatly swollen, and there was diffuse vesiculation over the lower portion of the abdomen and the thighs.

Urinalysis showed 4 plus albumin, a specific gravity of 1.018, 4 to 5 white blood cells, 1 or 2 red blood cells, no casts and many doubly refractive lipoids. Chemical examination of the blood showed: cholesterol, 584.6 mg.; chlorides, 364 mg.; total protein, 3.75 Gm.; albumin, 1.61 Gm., and globulin, 2.14 Gm., per hundred cubic centimeters. A blood count showed: hemoglobin, 70 per cent; red blood cells, 3,420,000, and white blood cells, 19,950. The renal function tests gave normal results.

During his stay in the hospital the patient had a series of severe infections. In September 1930 he had pneumonia followed by empyema. In October he had

erysipelas and after a prolonged course gradually recovered. In November the edema and albuminuria had completely disappeared. He made a complete and uneventful recovery.

This patient returns twice a year. Examination in August 1937 showed the urine, heart and blood pressure to be normal. He appeared to have recovered completely.

CASE 6.—A girl aged 7 years was admitted to the hospital on Dec. 19, 1935. One week before entrance, edema developed in the face, abdomen and extremities. A year and a half before entry she had a similar attack, which lasted several weeks. Both parents had chronic nephritis. The patient had had whooping cough, pneumonia, chickenpox and measles.

Physical examination revealed a well developed, well nourished and very edematous girl. The heart and lungs were normal. The eyegrounds were normal. The blood pressure was 120 systolic and 60 diastolic.

Urinalysis showed 4 plus albumin, a specific gravity of 1.025, an occasional red blood cell, 3 to 4 white blood cells and no casts. Chemical examination of the blood showed cholesterol, 530 mg.; total protein, 3.93 Gm.; albumin, 1.49 Gm., and globulin, 2.44 Gm., per hundred cubic centimeters. The blood counts were normal, and the sedimentation rate was rapid.

The output of fluid was low, but it gradually increased during the course of treatment. The edema disappeared, and the patient's condition became so satisfactory that she was discharged six weeks after entrance.

The patient was last examined on Aug. 11, 1937. She was free from all evidences of renal disorder and appeared to be in good condition.

CASE 7.—A man aged 34, was first seen on April 19, 1932. He had always been well and had worked as a railroad switchman until about four months prior to entry, when he began to notice that his ankles and face, especially around the eyes, were swollen in the morning when he arose. For a number of weeks the swelling had disappeared after several hours of activity. Then the edema became more pronounced and failed to subside. During March and April he was so edematous that he was unable to get out of bed.

The family history was irrelevant, and the patient's past history was uneventful except for measles at the age of 9 years and numerous attacks of infection of the upper respiratory tract.

Physical examination revealed a well developed and strong man whose only difficulty was generalized anasarca. The heart, lungs, abdomen and eyegrounds were normal. The blood pressure was 132 systolic and 80 diastolic. There was no arteriosclerosis.

Urinalysis showed 4 plus albumin, an occasional red blood cell, numerous hyaline casts and many doubly refractive lipoids. Chemical examination of the blood showed: cholesterol, 484 mg.; nonprotein nitrogen, 36.6 mg.; creatinine, 1.6 mg.; total protein, 4.92 Gm.; albumin, 1.8 Gm., and globulin, 2.95 Gm., per hundred cubic centimeters. A phenolsulfonphthalein test showed 75 per cent excretion in two hours. Except for signs of mild anemia the blood count was normal. The Wassermann reaction was negative.

In May 1933 the edema gradually subsided. Albuminuria and some edema about the face and ankles persisted during the entire summer of that year. Sometime early in the fall of 1933 the albuminuria disappeared and never returned. The cholesterol content of the blood dropped to 260 mg. per hundred cubic centimeters, and the albumin-globulin ratio returned to normal.

Observations made on this patient during 1935, 1936 and 1937 showed no evidences of renal disorder. The patient has worked steadily since 1933 and has had no ill effects from the disease.

CASE 8.—The patient, a boy aged 3 years, was admitted to the hospital on May 25, 1937. Two months before entrance there was a gradual onset of generalized edema. No sign of infection of the upper respiratory tract was noted before the edema developed, and there were no convulsions. The past history showed none of the usual diseases of childhood, and the patient had not been subject to infections of the upper respiratory tract.

Physical examination revealed a fairly well developed, pale boy. There was marked pitting edema involving the entire body. The abdomen was distended with fluid. The blood pressure was 100 systolic and 78 diastolic. Otherwise there were no significant findings.

Urinalysis showed 4 plus albumin, a specific gravity of 1.017, 2 to 3 white blood cells and no red blood cells. Chemical examination of the blood showed: cholesterol, 416.6 mg.; total protein, 4.98 Gm.; albumin, 3.12 Gm., and globulin, 1.86 Gm., per hundred cubic centimeters. Seventeen grams of protein was excreted in twenty-four hours. The sedimentation rate was 100 mm. in one hour. Renal function tests gave practically normal results.

The patient became very edematous. Marked distention of the abdomen followed, and fever developed. A diagnosis of pneumococcic peritonitis was made. The temperature rose to 103 F. The patient became comatose and died on June 10.

The primary cause of death as determined at autopsy was generalized pneumococcic peritonitis, and the contributory cause was lipoid nephrosis.

Gross Postmortem Description.—The right kidney measured 10.5 cm. in length, 5 cm. in width and 3 cm. in thickness and weighed 90 Gm. The capsule stripped easily, exposing a pale external surface, on which the stellate veins were extremely dilated. On cut section the parenchyma appeared to be pale yellow. It averaged about 20 mm. in thickness, of which 7 mm. was cortical tissue. The markings of the kidney were absent, and there was only a bright red streaking of the medullary portion. The pelvis showed a slightly congested mucous membrane and emptied into two ureters, which fused about at the level of the lower pole of the kidney into a single ureter.

The left kidney measured 10 cm. in length, 5 cm. in width and 3 cm. in thickness and weighed 80 Gm. The gross appearance of the left kidney externally was much the same as that of the right. On cut section the parenchyma averaged 20 mm. in thickness, of which 5 mm. was cortical tissue. The gross structure on the cut surface was essentially the same as that of the right kidney. Both kidneys were of doughy consistency.

Microscopic Postmortem Description.—The glomeruli studied in various sections were fairly normal in appearance. In a few, however, there was a slight proliferation of epithelial cells. Sections studied with the azocarmine stain showed no definite thickening of the basement membrane of the capillaries. There was no deposit of fatty substance within the glomeruli. The convoluted tubules showed swollen, granular and vacuolated epithelial cells, which in general appeared lightly stained. Some of the epithelial cells lining the tubules showed extensive swelling, and in some of them the nuclei could not be recognized. In some areas the epithelial cells of the convoluted tubules showed an increased number of mitotic figures. Sections stained for fat revealed an accumulation of minute droplets of fat in the basal portion of the epithelial cells. This deposit was not uniform and was not seen throughout all the tubules. On examination with the polarizing microscope this fat was anisotropic. The lumen of the tubules contained granular amorphous material. In other areas some of the tubules contained a homogeneous colloid-like

substance. The interstitial tissue of the kidney was free from cellular infiltration. The veins of the interstitial tissue were somewhat congested. The arteries showed no abnormal thickening or sclerotic processes.

CASE 9.—The patient, a boy aged 3 years, entered the hospital in December 1935, suffering from generalized anasarca. The edema, which began in September, came and went but gradually became worse until, on the day of entrance, he was too edematous to walk.

Physical examination revealed a well developed and well nourished boy. The heart and lungs were normal. The abdomen was distended with fluid, and the eyelids, extremities and genitalia were badly swollen.

Urinalysis showed 4 plus albumin, a specific gravity of 1.034, no red blood cells, several pus cells, granular casts and many doubly refractive lipoids. Chemical examination of the blood showed: cholesterol, 503 mg.; nonprotein nitrogen, 24.7 mg.; plasma protein, 3.08 Gm.; albumin, 1.37 Gm., and globulin, 1.71 Gm., per hundred cubic centimeters. Except for evidence of mild secondary anemia the blood counts were normal.

The edema disappeared after three months of treatment in the hospital. In April the patient returned home and was free from edema during the spring and summer of 1936. Moderate albuminuria persisted.

On Oct. 16, 1936, he was so edematous that hospitalization was again necessary. Physical examination showed no deviation from the former record. Urinalysis revealed marked albuminuria, a specific gravity of 1.024, no red blood cells, a few pus cells, a few casts and many doubly refractive lipoids. Chemical examination of the blood showed cholesterol, 608 mg.; nonprotein nitrogen, normal content; total protein 2.97 Gm.; albumin, 1.60 Gm., and globulin, 1.07 Gm., per hundred cubic centimeters.

The patient remained under observation in the hospital for some time. The marked albuminuria persisted for several weeks. The edema fluctuated in intensity during 1937. At present it has disappeared, and the patient appears to be recovering.

ANALYSIS OF CLINICAL DATA

Although lipoid nephrosis may occur at any age, it is rare after the age of 40 and develops most frequently in children and adolescents. The ages of the patients in this series ranged from 3 to 34 years; 6 were between 17 and 34 years of age, and 2 were 3 years old. There were 6 males and 3 females. There was no correlation between the age of the patient and the outcome of the disease. The first patient was aged 21 and died of a convulsion, with generalized edema, while the eighth patient was aged 3 and died of pneumococcic peritonitis. It may be that resistance to pneumococcic infection is lower in children than in adults. In no case was the etiologic factor definitely established. A summary of the essential data in these cases is given in table 1.

In no case was there the acute abrupt onset described by Blackman [15] and others. The disorder apparently began insidiously with edema of the face and ankles and gradually developed into generalized anasarca.

15. Blackman, S. S., Jr.: Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis: Clinical and Anatomical Studies, Bull. Johns Hopkins Hosp. **55**:1, 1934.

TABLE 1.—*Summary of Clinical Data*

Case No.	Patient's Initials; Date	Age	Urine						Blood Pressure, Mm. Hg	Edema	Blood					Renal Function			Comment
			Albumin	Specific Gravity	Red Blood Cells	White Blood Cells	Casts	Lipoids			Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.	Albumin-Globulin Ratio*	Phenolsulfonphthalein Test, % in 2 Hr.	Dilution and Concentration Test	Urea Clearance Test, %	
1	J. H.																		
	10/24/24	21	++++	1.023	0	Few	Few	++++	110/60	++++	22.0	1.5	.....	25.6	.....	50	1.003-1.025	....	
	12/ 1/25	22	++++	1.025	0	Few	Few	++++	120/75	++++	20.0	2.3	806.0	30.9	.....	65	1.005-1.027	....	
	2/10/26	23	++++	.....	0	...	...	++++	120/70	++++	16.8	1.7	555.0	28.5	.....	55	1.003-1.027	....	Died
2	H. Z.																		
	11/ 7/22	25	+++	.....	0	Few	Hyaline	0	120/80	++++	16.8	1.4	.....	31.6	.....	65	1.002-1.028	....	
	12/ 5/25	28	++	1.024	0	Few	...	++++	116/75	++	18.0	1.8	384.0	29.7	.....	..	.....	....	
	6/21/30	33	0	.....	0	...	0	0	.....	0	....	...	188.0	....	.....	..	1.004-1.026	....	
	11/23/35	38	0	.....	0	...	0	0	.....	0	....	...	.....	....	.....	..	.....	41.6	
	8/ 5/37	40	0	.....	0	...	0	.....	132/80	0	....	...	.....	....	.....	..	.....	....	Recovered
3	F. K.																		
	12/ 9/25	24	+++	1.020	0	Few	...	+++	125/75	++++	18.0	1.7	666.6	42.5	.....	60	1.006-1.030	....	
	1/19/26	25	+++	1.018	0	...	...	+++	130/80	++	12.0	...	374.0	....	.....	75	.....	....	
	3/ 1/26	25	+++	1.022	0	0	...	0	115/80	0	20.0	1.9	588.0	....	.....	..	.....	....	
	11/ 7/31	31	0	.....	0	0	...	0	120/80	0	....	...	180.0	....	.....	65	.....	43.5	
	5/22/37	37	0	1.025	0	0	...	0	122/70	0	....	...	.....	....	.....	..	.....	....	Recovered
4	S. M.																		
	1/24/25	32	++++	1.010	0	1-2	Occasional hyaline	++++	118/60	++++	14.0	2.7	362.9	32.7	.....	55	1.001-1.022	....	
	6/ 6/27	34	+	1.007	0	0	0	++	110/70	0	23.8	1.7	196.0	36.1	T.P., 6.00 Alb., 4.40 Glob., 2.78	75	1.003-1.021	40.8	
	8/10/34	41	+	1.020	0	0	0	0	120/80	0	....	...	.....	....	.....	..	.....	....	Recovered
5	C. L.																		
	7/26/30	18	++++	1.018	1-2	4-5	0	++	112/70	++++	18.2	1.4	548.6	31.5	T.P., 3.75 Alb., 1.61 Glob., 2.07	40	1.005-1.010	....	
	9/ 9/30	18	++	1.025	0	0	0	0	108/78	0	26.6	1.9	211.0	37.0	T.P., 6.07 Alb., 4.00 Glob., 2.07	65	1.002-1.025	....	
	10/30/30	18	0	1.021	0	0	0	0	110/62	0	....	1.3	138.0	32.6	.....	55	1.001-1.022	....	
	8/ 2/37	25	0	1.023	0	0	0	0	110/70	0	....	...	.....	....	.....	..	.....	....	Recovered

6	D. S.																		
	12/21/35	7	++++	1.025	1-2	3-4	0	++++	122/68	++++	16.8	1.6	530.0	33.4	T.P., 3.93 Alb., 1.49 Glob., 2.44	80	1.001-1.030	44.3	
	2/18/36	8	++++	1.015	2-3	0	0	++++	105/70	0	15.4	1.5	333.3	27.7	T.P., 4.34 Alb., 2.04 Glob., 2.30	80	1.002-1.027	42.84	
	3/ 3/36	8	++	1.020	2-3	0	0	++	100/80	0	14.0	1.5	277.7	28.2	T.P., 5.15 Alb., 2.80 Glob., 2.35	75	1.008-1.028	....	
	6/23/37	9	0	1.026	1	2-3	0	0	100/60	0	....	...	.....	.....	T.P., 7.24 Alb., 4.10 Glob., 2.55	..	1.010-1.026	....	
	8/11/37	9	0	.....	0	0	0	0	.....	0	....	..	.....	....	.....	..	.....	....	Recovered
7	H. C.																		
	4/ 9/32	34	++++	1.022	Occ.	3-4	Hyaline	+++	132/80	++++	....	1.6	484.0	36.8	T.P., 4.92 Alb., 1.80 Glob., 2.95	75	1.006-1.028	....	
	6/ 4/33	35	+	1.020	0	0	0	0	130/80	0	....	...	260.0	....	T.P., 6.80 Alb., 4.00 Glob., 2.50	65	.....	....	
	10/25/35	37	0	1.024	0	0	0	0	136/84	0	....	...	.....	.....	.....	..	.....	....	
	7/10/37	39	0	.....	0	0	0	0	.....	0	....	...	.....	....	.....	..	.....	....	Recovered
8	A. P.																		
	5/27/37	3	++++	1.017	0	2-3	0	++++	100/78	++++	14.0	1.3	416.6	27.7	T.P., 4.98 Alb., 3.12 Glob., 1.86	..	.....	....	
	6/ 1/37	3	++++	1.035	0	2-3	Many, granular	++++	115/84	++++	18.8	1.3	382.8	29.7	T.P., 4.31 Alb., 1.98 Glob., 2.33	..	.....	....	
	6/ 8/37	3	++++	1.017	0	2-3	Many, granular	++++	105/80	++++	25.8	1.6	384.6	46.1	T.P., 4.50 Alb., 2.40 Glob., 2.10	..	....	...	Died of pneumococcic peritonitis
9	A. S.																		
	12/10/35	3	++++	1.034	0	0	Few	.....	.....	++++	....	...	503.0	....	.....	..	.....	....	
	1/ 8/36	3	+++	1.024	0	7-8	Many, granular	+++	100/60	+++	....	...	608.0	24.7	T.P., 3.08 Alb., 1.37 Glob., 1.71	..	1.008-1.030	....	
	12/24/36	3	++	.....	1-2	3-4	...	.....	.....	+++	....	...	.....	.....	T.P., 2.97 Alb., 1.60 Glob., 1.07	..	.....	....	
	6/ 9/37	4	+++	1.026	...	Few	...	.....	.....	++	....	...	.....	.....	.....	..	.....	....	Progress satisfactory

* T.P. indicates total protein; Alb., albumin; Glob., globulin.

The results of chemical examinations of the blood and other laboratory data are tabulated in table 1. These results conform to data published regarding other cases of lipoid nephrosis. Hypercholesteremia, inversion of the albumin-globulin ratio and the absence of nonprotein nitrogen or of creatinine retention were features of every case. The ability to concentrate was normal, and no insufficiency was found with the phenolsulfonphthalein or the urea clearance test. In no instance was there arteriosclerosis of the peripheral arteries, hypertension, retinitis or cardiac hypertrophy. The Wassermann reaction was negative in all cases.

Albuminuria was marked, the amount of albumin excreted varying from 5 to over 45 Gm. a day during the active period of the disease. This excessive loss of albumin was closely related to the deficit of plasma protein and the onset of edema. The specific gravity of the urine was high, ranging from 1.017 to 1.035. The urinary sediment in no case contained more than an occasional red blood cell, but white blood cells and waxy casts were common features. Doubly refractive lipoids were found with the polarizing microscope in every case, but the number and size bore no relation to the degree of edema. It was not uncommon to find them in the urine months after the edema had subsided. When albuminuria disappeared, anisotropic lipoids were not in evidence.

The outstanding feature was the edema, which followed practically the same pattern in every case. It came on gradually and painlessly and within a few weeks disappeared without causing the patient much discomfort, only to return weeks or months later. The recurrent attacks were more severe and resistant to treatment than the original ones, and in some cases the swelling assumed tremendous proportions. Although edema is a constant feature, it must be borne in mind that it is intermittent. Many believe that this symptom constitutes lipoid nephrosis, but the disease may persist for many years, as is seen from observations recorded here, and yet edema may be prominent for only a short period.

Examinations of the protein content of the blood plasma were made in all cases except cases 1 to 3. The onset and remissions of attacks of edema were closely related to changes in the plasma protein content. In case 4 a determination of the quantities of total protein and albumin was not made during the period of edema. Our observations are in accord with the view of Moore and Van Slyke,[16] who have pointed out that patients with a low plasma protein content show a tendency to

16. Moore, N. S., and Van Slyke, D. D.: The Relationships Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

edema formation. Our examinations show that there is no exact parallelism between the onset of edema and the decrease of the plasma protein content. This is particularly emphasized in case 8. The lack of correspondence is undoubtedly due to the fact that the colloidal osmotic pressure of the blood plasma does not always conform to the changes in the quantity of plasma protein.

Hypertension was not observed during the course of the disease. When in a case considered at first to be one of lipoid nephrosis, hypertension developed, even though mild in type, other symptoms of chronic glomerulonephritis invariably followed.

From the clinical point of view the study of these cases over a number of years has led to an understanding of the true course and outcome of lipoid nephrosis that cannot be afforded by short periods of observation. One patient (case 2) was studied for fifteen years, 2 (cases 3 and 4) for twelve years each, 1 (case 5) for seven years, 1 (case 7) for five years, 2 (cases 6 and 9) for two years each, 1 (case 1) for one and a half years and 1 (case 8) for three months. A summary of the data on the clinical course and outcome is given in table 2.

TABLE 2.—*Summary of Data on Clinical Course and Outcome*

Case	Age at Onset	Sex	Length of Time Studied	Duration of Symptoms	Period Free from Symptoms	Outcome
1	21	M	1½ years	1½ years	.....	Died
2	25	F	15 years	4 years	12 years	Recovered
3	24	M	12 years	2 years	10 years	Recovered
4	32	F	12 years	3 years	7 years	Recovered
5	18	M	7 years	8 months	6 years	Recovered
6	7	F	2 years	6 months	1½ years	Recovered
7	34	M	5 years	1½ years	3½ years	Recovered
8	3	M	3 months	3 months	.....	Died
9	3	M	2 years	2 years	.....	Under observation

ANALYSIS OF PATHOLOGIC DATA

The pathologic changes observed at autopsy in cases of lipoid nephrosis are most pronounced in the tubules of the kidney. It should be emphasized, however, that in many cases the glomeruli as well as the tubules are affected—the so-called glomerulonephrosis of Fahr.[12] This fact does not imply that nephrosis represents involvement of either the glomeruli or the tubules alone but rather involvement of the entire functional unit of the kidney—the nephron.

Various authors who have studied the morphologic changes in the glomeruli disagree as to whether the lesion is inflammatory or degenerative and whether or not glomerular change can be demonstrated in every case clinically typical of lipoid nephrosis. The morphologic changes in the glomeruli involve, if demonstrable, the basement membrane, the capillary endothelial cells and the glomerular epithelial cells.

In the early stages of lipoid nephrosis, it is generally agreed, there is no circulatory disturbance within the glomerular capillaries (Volhard,[17] Shaw Dunn [10] and Bell [9]), but one must assume a functional disturbance of the capillaries, evidenced by increased permeability. This is not necessarily accompanied in the early phase by damage to the histologic structure of the glomerulus but may later lead to morphologic changes which are described as representing glomerulonephrosis. There seems to be a parallelism between the extent of the glomerular damage and the duration of the increased permeability as well as the chemical and physical nature of the protein passing through the capillary wall.

If one summarizes the glomerular changes in lipoid nephrosis, two phases can be recognized: (*a*) an early stage, in which there is only an increased permeability of the capillaries, with no demonstrable morphologic lesion in the glomerular structure, and (*b*) a later stage, in which the increased permeability has produced changes in the basement membrane, the capillary endothelial cells and the epithelial cells of the glomerulus, the typical picture of so-called glomerulonephrosis. The changes observed in the cases studied here may be summarized as follows:

1. The involvement of the glomeruli was not uniform and was not of the same nature as the microscopic lesion observed in glomerulonephritis. A slight but not uniform thickening of the basement membrane of the capillaries was found in an occasional glomerulus. Infiltration of the glomerular cells by fatty substances was not an outstanding feature.

2. Changes in the tubules, especially in the proximal portion of the convoluted tubules, were the most outstanding features. There were deposits of fatty substances near the basilar portion of the epithelial cells which showed doubly refractive properties on examination with the polarizing microscope. Besides the deposit of fat or lipoid material, the epithelium showed evidence of various other so-called degenerative processes, consisting of hyaline droplet infiltration and hydropic degeneration.

3. The lumens of the tubules were irregular and often contained an amorphous granular material, occasionally with some doubly refractive granules and a homogeneous colloid-like substance.

4. The interstitial tissue of the kidney did not present any inflammatory reaction.

5. Vascular changes in the large, medium-sized and small arteries were absent.

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17. Volhard, F., in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 2, p. 1046.

Dr. Bell [18] studied the kidney in case 8 and observed no structural change in the glomeruli. His opinion was that the appearance of the tubules supported our interpretation of lipoid nephrosis.

COMMENT

The main stumbling block in the recognition of lipoid nephrosis is the fact that many patients with chronic glomerulonephritis present an almost identical clinical picture. Histologically, however, the difference is easily apparent, even though there may be minimal glomerular involvement. If there is extensive tubular degeneration with scant glomerular disease, the nephrotic syndrome is likely to be most prominent clinically; on the other hand, if glomerular lesions predominate, the classic picture of glomerulonephritis prevails. Frequently there is a mixture of the two, and sometimes the nephrotic changes so dominate the picture that a diagnosis of lipoid nephrosis is erroneously made.

Contrary to the opinion of some observers, the controversy concerning the identity of lipoid nephrosis has not been settled but only laid aside until further investigation clears up the problem. Uncertainty and confusion still surround some of the most important aspects of the disease, particularly the nature of the glomerular changes. There is almost complete agreement regarding the lipoid degeneration of the tubular epithelium, but this is not true of the malpighian tufts. Formerly the glomeruli were described as normal, but more recently Fahr,[12] Munk,[19] Volhard,[17] Fishberg [20] and others have described degenerative changes in the endothelium and epithelium corresponding to those seen in the tubular epithelium but of lesser degree. There are writers like Shaw Dunn [10] who consider the changes in the glomeruli as larval forms of glomerulonephritis. Likewise, Bell [9] has stated that the structural changes in the basement membrane of the glomerular capillaries which are revealed by a special stain represent a stage of glomerulonephritis.

After making examinations in 2 cases of lipoid nephrosis with the newer special stains, Kantrowitz and Klemperer [21] concluded that the slight swelling of the endothelial cells and the thickening of the base-

18. Bell, E. T.: Personal communication to the authors.

19. Munk, F.: Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren: Einführung in die moderne klinische Nierenpathologie, ed. 2, Berlin, Urban & Schwarzenberg, 1925.

20. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1934.

21. Kantrowitz, A. R., and Klemperer, P.: Ueber Lipoidnephrose, Virchows Arch. f. path. Anat. **280**:554, 1931.

ment membrane do not signify inflammation. Hitzrot and Read [22] also have presented evidence that lipoid nephrosis is a clinical and pathologic entity. In their cases the clinical features of glomerulonephritis were absent, and after exhaustive histologic studies, using the staining methods advocated by Bell,[9] they found no indications of inflammatory lesions.

Since the earlier studies by Munk,[4] Volhard and Fahr,[5] Epstein [6] and others the problem concerning the individuality of lipoid nephrosis has been widely discussed. Earlier pathologists, Aschoff,[3] Löhlein [2] and Schlayer,[23] denied its existence. Aschoff [3] contended that a complete separation of nephrosis from nephritis is not warranted because of the histologic changes in the kidney. He stated that most of the cases of nephrosis turn out to be cases of chronic glomerulonephritis. Löhlein [2] supported the idea that so-called lipoid nephrosis is the sequel to antecedent glomerulonephritis, although he had the opportunity of examining a kidney from a patient with lipoid nephrosis in which there was no conclusive evidence of preceding glomerulitis. Munk,[4] who suggested the term lipoid nephrosis, was also responsible for the theory that the changes in the kidney are secondary to a general metabolic disturbance affecting cholesterol metabolism. The term nephrosis was adopted by Volhard and Fahr [5] to include the degenerative diseases of the kidney as distinct from the inflammatory diseases. Its popularity grew rapidly until it has now become well established and its position in the classification of Bright's disease is secure.

In England the term has not been accepted as generally as it has in Germany and America; yet Bennett [24] has concluded that lipoid nephrosis exists. Gainsborough [8] said he found no justification for regarding it as a separate entity, because he saw that patients considered clinically to have lipoid nephrosis showed the features of chronic glomerulonephritis at autopsy. In his opinion there is no dividing line between the two conditions, but he has concluded that the term nephrosis may be conveniently used to describe certain syndromes of nephritis. In the opinion of Shaw Dunn,[10] in typical cases of nephrosis the glomeruli may present only slight histologic changes. It is difficult to say whether such authorities as Löhlein [2] and Fahr [12] would consider the glomeruli completely normal; yet it appears doubtful to many whether changes so slight and elusive can possess much pathogenic significance, especially when tubular lesions are much more pronounced. After careful analysis of 9 cases, Shaw Dunn concluded that nephrosis is probably a subdivision of subacute glomerulonephritis.

22. Hitzrot, L. H., and Read, W. T., Jr.: Clinical and Pathological Studies in a Case of Pure Lipoid Nephrosis, Am. J. M. Sc. **185**:233, 1933.

23. Schlayer: Ueber die Nephrose, Med. Klin. **14**:53, 1918.

24. Bennett, T. I.: Nephrosis, Lancet **1**:115, 1931.

The differentiation of lipoid nephrosis from chronic glomerulonephritis in this country seemed to be fairly well established until Bell,[9] in 1929, began to cast doubt on its individuality. He was the chief sponsor of the idea that all patients with pure lipoid nephrosis show some degree of glomerulitis and that the disease affects the capillaries of the glomerular tuft. This opinion is based on the fact that with special technic a decided thickening of the basement membrane of the capillaries and an increase in the number and in the size of the endothelial cells in the glomerular tuft can be found after, most likely, an initial injury to the glomerular capillaries by some toxic agent. He concluded that lipoid nephrosis is to be regarded as a form of glomerulonephritis in which the glomeruli are damaged but their capillaries are only partially destroyed, so that they continue to function and tubular atrophy does not occur.

The weight of Christian's [7] opinion caused many clinicians to accept the position that lipoid nephrosis is only a stage in the course of glomerulonephritis. After a review of his large clinical experience he concluded that the term might be useful to designate a syndrome but that the condition is not a definite pathologic entity. He stated that there have been few clinical reports which show the ultimate outcome in cases of so-called lipoid nephrosis.

Clinical and pathologic investigation led Blackman [25] also to conclude that lipoid nephrosis is a form of diffuse nephritis with particular clinical and anatomic characteristics. This condition may persist for long periods, at least in children, without the development of the destructive lesions in the majority of the glomerular tufts which multiply progressively during the course of subacute and chronic glomerulonephritis. Blackman collected evidence from classic examples described in the literature and from 10 cases of his own to show that nephrosis is a particular form of diffuse nephritis in which microscopic hematuria, anemia, slight elevation of the blood pressure and a high nonprotein nitrogen content of the blood may all be found. The histologic lesions in the kidney consist chiefly of certain diffuse changes in the epithelium of the glomeruli and tubules identical with those which may occur in any form of nephritis. He emphasized that no changes in the glomerular capillaries can be recognized to account for the excretion of albumin in the urine. The most important histologic distinction between nephrosis and nephritis is the lack of coagula containing fibrin within the glomerular capsule in nephrosis. In the absence of these, clot organization and scar tissue formation, with the degeneration of the glomeruli and progressive renal insufficiency, do not occur. The mechanism

25. Blackman, S. S., Jr.: On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, Bull. Johns Hopkins Hosp. **57**:70, 1935.

responsible for this difference in the two diseases has not been fully determined. Blackman concluded that there is no evidence that lipoid nephrosis is a metabolic disease.

The data for approximately 160 patients at the Mayo Clinic who presented the "nephrotic syndrome" were reviewed by Bannick.[26] In 30 cases a diagnosis of lipoid nephrosis was justified at the time of entry. Most of the patients were followed after leaving the clinic. Seven were apparently cured; 9 described their condition as "fine," but laboratory data were not given; 4 were markedly improved but not cured; 2 were better but had glomerulonephritis; 1 showed no improvement, and 7 died, apparently with chronic glomerulonephritis. Bannick stated the belief that the insidious onset of lipoid nephrosis with the high proportion of patients who have had it for years makes the clinical course different from that of ordinary nephritis and provides a basis for the theories of those who claim that it is a distinct entity. He also stated that this argument is easily met with one based on the fact that in some of these cases definite glomerulonephritis develops and the patient dies in uremia. If glomerulonephritis can be proved to have developed in 7 of 30 cases of lipoid nephrosis, there must be an intimate relation between the two conditions. He concluded, however, that from the clinical standpoint there is justification for separating a group of patients with lipoid nephrosis from those with ordinary nephritis in order to clarify the problem of the renal pathologic and physiologic status in general. Boyd,[27] too, said he regarded nephrosis as a form of glomerulonephritis in which the glomerular capillaries are damaged but not completely obscured.

It must not be thought, however, that all authorities have repudiated the concept that nephrosis is a disease distinct from glomerulonephritis. Leiter[13] said: "In its primary uncomplicated form this syndrome is known as nephrosis and is a rare disease. The rarity of the disease is no justification for the denial of its existence." He emphasized the keynote of the difficulty in differentiating nephrosis from glomerulonephritis when he said, "The nephrotic type of glomerulonephritis can mimic down to the last detail the entire clinical complex of signs and symptoms of nephrosis."

In an after-study of lipoid nephrosis Major[28] presented 6 cases. Two of the patients died, both showing at autopsy marked evidences of chronic glomerulonephritis. Three apparently made a complete

26. Bannick, E. G.: Lipoid Nephrosis and Its Relation to Glomerular Nephritis, J. A. M. A. **102**:172 (Jan. 20) 1934.

27. Boyd, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1932, p. 437.

28. Major, R. H.: After-History of Lipoid Nephrosis, Am. J. M. Sc. **191**:43, 1936.

recovery and were observed over a long enough period to substantiate the clinical diagnosis.

From the clinical standpoint Stone [29] said he believed there is ample reason to retain the identity of this little known lipoid form of Bright's disease, since it is distinguished from other main types by certain particular features. Stone stated that about 20 per cent of the patients with lipoid nephrosis may recover after a period of invalidism lasting from a few months to a year or more. In about 20 per cent death will occur from exhaustion or malnutrition, and 50 to 60 per cent will die from terminal streptococcic or pneumococcic peritonitis. After a comparison of Stone's experience with our own it appears that the prognosis was much better in our series.

Shapiro [30] has emphasized his belief that pure lipoid nephrosis does exist and has cited a case in which there was no evidence of glomerulonephritis. He said he believed that even if some glomerular changes, such as swelling of the epithelium of Bowman's capsule and lipoid degeneration of the glomerular tufts, are noted, a degenerative rather than an inflammatory process is signified and, furthermore, that the finding of an occasional glomerulus showing a definite inflammatory reaction does not constitute the picture of glomerulonephritis.

Five patients presenting the clinical signs of the nephrotic syndrome were reported on by Landis and Elsom.[31] By using the Addis method they pointed out that 3 showed no clinical signs of glomerulonephritis and excreted from 200,000 to 800,000 erythrocytes in twelve hours, and 2, with clinical signs of subacute glomerulonephritis, excreted 4,000,000 erythrocytes in twelve hours.

After studying various forms of nephritis Terbrüggen [32] concluded that lipoid nephrosis exists as a disease entity. He reported the case of a boy aged 2½ years who died of pneumococcic peritonitis. At autopsy the glomeruli showed no adhesions of the capillaries, and the endothelial cells in only a few loops were swollen. Particular attention was paid to the basement membrane of the capillaries, but widening and swelling could not be demonstrated with ordinary or special azo stains. There were no morphologic changes that were typical of glomerulonephritis. He said he did not believe that there is a primary glomerulonephritis but that a toxin increases the permeability of the glomerular capillaries.

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29. Stone, W. J.: Bright's Disease and Arterial Hypertension, Philadelphia, W. B. Saunders Company, 1936.

30. Shapiro, P. F.: Lipoid Nephrosis: Pathology, Genesis and Relation to Amyloidosis, Arch. Int. Med. **46**:137 (July) 1930.

31. Landis, E. M., and Elsom, K. A.: The Nephrotic Syndrome in Adults, Internat. Clin. **1**:1, 1937.

32. Terbrüggen, A.: Degeneration, Speicherung und Nephrose, Klin. Wchnschr. **14**:1305 and 1345, 1935.

In the opinion of Matthew and Cameron [33] the primary renal change in lipoid nephrosis is the increased permeability of the capillary membrane which allows substances of unusually large molecular content to escape from the blood. They suggested, too, that nephrosis is merely syphilis of the kidney.

Elias [34] said he recognized the existence of lipoid nephrosis anatomically. He concluded that it is due to some chronic infectious disease such as syphilis, malaria or tuberculosis.

Among the recent publications of great importance on the subject of lipoid nephrosis is the article by Randerath.[11] He observed that the glomerular epithelial cells show cloudy swelling or hyaline degeneration in addition to thickening of the basement membrane of the capillaries. Various loops of the glomeruli are affected in later stages, and widening and swelling of the capillary wall of the glomeruli and the parietal covering of the capsule are seen. There may also be hyaline clumping of the glomerular loops. In summarizing, Randerath said that the primary change in lipoid nephrosis is increased permeability of the glomerular capillaries, occurring with or without demonstrable damage to the capillary wall and leading to secondary changes in the tubular epithelium and glomeruli.

A recent review of the question of lipoid nephrosis by Fahr [12] is also interesting. He has emphasized again that true lipoid nephrosis is fundamentally different from glomerulonephritis and that although there is difficulty in differentiating between the two conditions, the belief that they are distinct is growing. The lesions in the glomeruli are not inflammatory and are best described as indicative of "chronic glomerulonephrosis."

Analysis of our 9 cases has led us to believe that lipoid nephrosis is fundamentally different from glomerulonephritis and that patients in whom nephritic symptoms develop never have had true nephrosis. Histologic examination in 2 cases showed the characteristic features of lipoid nephrosis. There were no evidences of inflammation in the glomeruli, but degenerative changes were seen in the endothelial and epithelial cells of the tuft. Obviously we were unable to determine whether or not thickening of the basement membrane might develop later, as emphasized by Fahr.[35]

We agree with those authorities who say that nephrosis is often simulated by chronic glomerulonephritis but that the primary form of the disease is seldom seen. The lack of autopsy material, however, has

33. Matthew, E., and Cameron, J. D. S.: Chronic Nephrosis, Edinburgh M. J. **40**:569, 1933.

34. Elias, H.: Ueber Nephrosen, Wien. klin. Wchnschr. **48**:1177, 1935.

35. Fahr, G.: What Is Lipemic Nephrosis? Am. J. M. Sc. **194**:449, 1937.

given an exaggerated view of its rarity because most patients recover. We have concluded that the slight changes occurring in the glomeruli are not inflammatory and do not indicate glomerulonephritis. Notwithstanding the differences of opinion regarding the significance of the minimal lesions, the fundamental fact remains that patients with such renal changes show a very different course from those with true glomerulonephritis. In spite of all the arguments advanced by those who have given this controversy careful consideration, we believe that the distinctive course and the favorable prognosis are sufficient grounds for retaining the term nephrosis in the classification of Bright's disease.

SUMMARY

A factor of fundamental importance in the clinical study of any form of Bright's disease is the length of time the patient has been observed. Lipoid nephrosis, more than any other form of Bright's disease, emphasizes that a long, detailed study and proper evaluation of signs and symptoms are necessary for an accurate diagnosis.

Our purpose in reporting this series of cases is (*a*) to show by histologic and prolonged clinical study that lipoid nephrosis is different from chronic glomerulonephritis with the nephrotic syndrome and that there is justification on clinical grounds alone for this distinction; (*b*) to establish lipoid nephrosis as a clinical and pathologic entity, in order to arouse further investigation into the cause of the hyperpermeability of the glomeruli for protein, the production of edema and the abnormal metabolism of cholesterol in these cases; (*c*) to show the practical importance of the fact that patients with lipoid nephrosis recover while those with chronic glomerulonephritis usually do not, and (*d*) to present a clinical study with prolonged observations and histologic examinations which may help to clarify some aspects of the controversy and may help to establish the individuality of lipoid nephrosis.

In this report 9 cases of genuine lipoid nephrosis are presented and discussed. Two patients died and were studied post mortem, 6 recovered completely and 1 is under observation. The period of study of these patients varied from three months to fifteen years. Most patients were observed longer than seven years.

The histologic examination of the kidneys of the 2 patients studied post mortem failed to show evidences of chronic glomerulonephritis. Degenerative changes characteristically described as features of lipoid nephrosis were present. In 1 case the special staining methods of Bell were used, and not even thickening of the basement membrane of the capillaries was observed.

A review of the theories of many of the prominent clinicians and pathologists who have made a study of lipoid nephrosis is given. It is

pointed out that the fundamental change in lipoid nephrosis is the hyperpermeability of the capillaries of the glomeruli. This functional disorder is associated with profound albuminuria followed by generalized edema. Whether or not this functional derangement is followed by a structural alteration is a problem to be determined in the future. A satisfactory explanation is lacking for this hyperpermeability.

This report tends to support the view that there is justification for the distinction between lipoid nephrosis and chronic glomerulonephritis. We believe that there are ample grounds for this because of the favorable prognosis in lipoid nephrosis as contrasted with the poor one in chronic nephritis. We conclude from our clinical and pathologic studies that although lipoid nephrosis is a rare disease compared with chronic nephritis, there is sufficient reason for maintaining the distinction of lipoid nephrosis in the classification of Bright's disease.

THROMBO-ENDOCARDITIS IN RABBITS

A NEW DISEASE DUE TO AN INFRAVIRUS (?)

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During the last five years, by means of numerous experiments, which have been reported separately in Italian reviews,[1] we have fully described from the anatomic, bacteriologic, macroscopic and microscopic standpoints a new disease that can be caused in rabbits by several experimental procedures.

We shall here summarize briefly what we have observed and deduced from our experiments as to the nature and genesis of this new disease. The starting point of our experiments was an attempt to transmit the infection which is the cause of rheumatic fever in man to young rabbits by injecting blood from infected persons. We noted that an endoperitoneal injection of 5 to 10 cc. of infected blood, freshly taken from the vein and unchanged by the addition of anticoagulant agents, frequently caused in the rabbit a morbid process, consisting essentially of thrombo-endocarditis, the morphologic features of which will be described later.

We obtained the same result, although less frequently, by using blood from nonrheumatic persons, and this made us doubt the possibility of having transmitted the rheumatic infection from man to animal. As a matter of fact, subsequent experiments showed that the blood of

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1. Andrei, G., and Ravenna, P.: (*a*) Experimental Researches on the Etiology and on the Pathogenesis of Rheumatic Fever, Acta rheumatol. **6**:12 (Dec.) 1934; (*b*) Ricerche sperimentali sulla eziologia e sulla patogenesi del reumatismo articolare acuto, Riv. di idroclimat., talassol. e terap. fis. **46**:166 (April) 1935; (*c*) Ricerche sulle infezione focali: La questione del tropismo elettivo degli streptococchi, Boll. d. Ist. sieroterap. milanese **13**:229 (April) 1934; (*d*) Ricerche sulle infezioni focali: La produzione sperimentale di lesioni simili a quelle del reumatismo articolare acuto, ibid. **13**:804 (Oct.) 1934; (*e*) Ulteriori ricerche sull'eziopatogenesi del reumatismo acuto e dell'endocardite sperimentale del coniglio, ibid. **14**:713 (Aug.) 1935; (*f*) Sulla natura ed il significato della tromboendocardite sperimentale del coniglio, ibid. **16**:138 (March) 1937.

healthy rabbits, normal and sterile horse serum and unskimmed and sterilized milk also, when used in the same manner, are likely to cause the disease in a number of cases.

TECHNIC

From 15 to 30 cc. of blood was drawn directly from the bend of the elbow and immediately injected with the same syringe into the peritoneal cavity of three or four rabbits in doses of from 5 to 6 cc. for each animal, without the use of any anticoagulant agent. When blood is quickly withdrawn and injected there is no time for it to coagulate. If rabbit blood in about the same amounts is obtained from the heart and injected directly, it is advisable to draw the blood in a syringe containing a small quantity of sodium citrate, as otherwise coagulation will occur quickly.

The horse serum used was the usual commercial serum contained in sterile ampules for injection; the dosage was practically the same as that used in the case of whole blood.

The blood filtrate was obtained by a special procedure, as we wished to filter the whole blood, not just the serum and the plasma, which, as is well known, are generally less rich in bacteria than is whole blood. Also the plasma obtained by strong centrifugation may be poorer in bacteria than is whole blood.

As far as is known, a total blood filtrate cannot be obtained, because the red blood cells obstruct the pores of the filter; neither can hemolyzed blood be filtered, since the stroma will act in the same manner. Therefore, to the blood rendered noncoagulable by the addition of 2 cc. of a 15 per cent solution of sodium citrate for each 20 cc. of blood, an equal amount of sterile physiologic solution of sodium chloride was added. Centrifugation at low speed was carried out for a few minutes in order to precipitate most of the red blood cells but not the white blood cells. Then the supernatant fluid, which was still rather thick, was collected and filtered through an L$_3$ Chamberland filter. By repeating the same procedure several times we thought that we obtained the hypothetic virus of the blood in the resulting fluid. The blood was filtered with Martin's apparatus, a suction of not over 60 cm. of mercury being used. The efficiency of the procedure was continually controlled by the addition of Bacillus prodigiosus, according to the usual bacteriologic technic, for in this manner the filtering of the fluid is accomplished more quickly. The filtrate obtained from 5 cc. of blood was injected into each rabbit, and two rabbits received injections at the same time of the same material.

For another series of experiments we made use of a suspension of endocarditic vegetations. To obtain the suspension we proceeded as follows: With a perfectly sterile technic, the thorax of the animal was opened as soon as it had been killed. The heart was removed and placed in a Petri dish. Then it was opened, and so far as possible contact with air was avoided. If endocarditic lesions were found, the valves and the thrombotic vegetations were removed, immediately triturated in a sterile mortar and suspended in a small quantity of sterile physiologic solution of sodium chloride, to be injected into the peritoneal cavity.

For our experiments we always made use of young rabbits, aged 30 or 45 days, but we wonder whether such a condition was essential. However, this was the starting point of our experiments, since we thought that young animals, which had never been used previously by other investigators, should be more sensitive to the hypothetic virus in question. Since we obtained positive results with young rabbits, we did not think it advisable to use old rabbits also; instead, we tried to work out more important details.

As will be shown later, positive results were obtained with a number of animals which had each received an injection about three weeks before; lesions of endocarditis were observed only exceptionally before this time. Nevertheless, we waited usually four to six weeks before killing the animals, since in this manner gross lesions were obtained.

Through transmission serially we obtained positive results using the blood and the endocarditic vegetations removed from animals which had been inoculated one or two months previously. The animals that had received injections were isolated with great care in eight different compartments. We did not think it a sufficient guaranty of isolation to put them in different cages, although many iron cages were at our disposal which could have been perfectly sterilized.

ANATOMIC DESCRIPTION

The most important form of the disease was thrombo-endocarditis, usually clearly evident although of varying intensity, affecting the right side of the heart, especially the tricuspid valve, and sometimes the walls of the ventricle and of the auricle, the tendinous cords and the papillary muscles. Lesions of the left ventricle were rarer, and only the mitral valve and its tendinous cords were ever involved. The most important lesion consisted of verrucous, gray, reddish gray or rose-colored thrombi which adhered tenaciously to the underlying tissue and were friable.

Macroscopically, the valves did not show any alteration other than an occasional gelatinous aspect, more usually of the mitral valve. Microscopically, the thrombi looked like white thrombi, having a stratified structure like that of a sand bed, which sometimes alternated with a layer of red thrombi. The substance forming them had either a fine reticular or homogeneous appearance, it stained well with eosin, it did not always respond to Weigert's test for fibrin and it usually contained a small number of white blood cells, mostly lymphocytes or polymorphonuclear pseudo-eosinophils.

The microscopic changes in the valves were rather scanty; more often than not the valve was thinner, without an endocardium in the part where the thrombus adhered, while at other times it was thick, with an edematous appearance.

The classic features of inflammation were nearly always absent, since, as is now well known, exudation of serum is considered by modern pathologists as the chief or the only evidence of inflammation.

Sometimes we noted slight hyperplasia of the valvular tissue, with some formation of blood vessels and with a considerable proliferation of the endocardium, so as to form a vegetation on the valves, which was seen at a glance to be granular. In one of the few cases in which we kept the animal alive many months after the injection, we observed sclerosis affecting the mitral valve and a tendinous cord, extending down to the corresponding papillary muscle; the newly formed connective

tissue still had the features of young tissue and showed considerable parvicellular infiltration.

The myocardium often remained exempt from lesions, and only in a few cases did we observe small nodular or diffuse infiltrations, constituted nearly always of elements of a lymphocytic type and of some polymorphonuclears, although epithelioid and plasma cells and rare giant cells sometimes were present. The muscular fibers when the infiltrations were small were only dissociated, but if the nodules were large

Fig. 1.—Endocarditic lesions (right ventricle) resulting from the injection of blood from a patient with rheumatic fever. The rabbit was killed sixty-three days after the intraperitoneal injection of 5 cc. of blood.

they also showed regressive changes which might reach hyaline degeneration and necrosis. However, we noted substantially similar lesions also in the myocardium of rabbits which had undergone different treatment, for instance, those which had been given injections of streptococcus cultures in the course of the experiments on focal infections.[1] Therefore, we do not think that these lesions stand in strict relation to the endocarditic lesions, considering the rarity and lack of parallelism

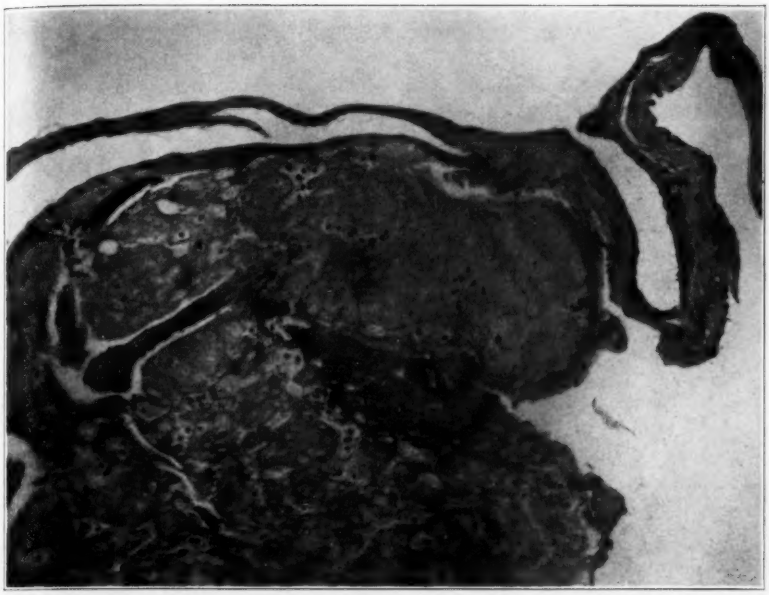

Fig. 2.—Slightly enlarged photomicrograph of a section of a large thrombus on the tricuspid valve of a rabbit killed forty-four days after the injection of blood from an endocarditic rabbit. Note the scantiness of the cellular elements contained in the thrombus and the thinness of the part where the thrombus adheres. Hematoxylin stain.

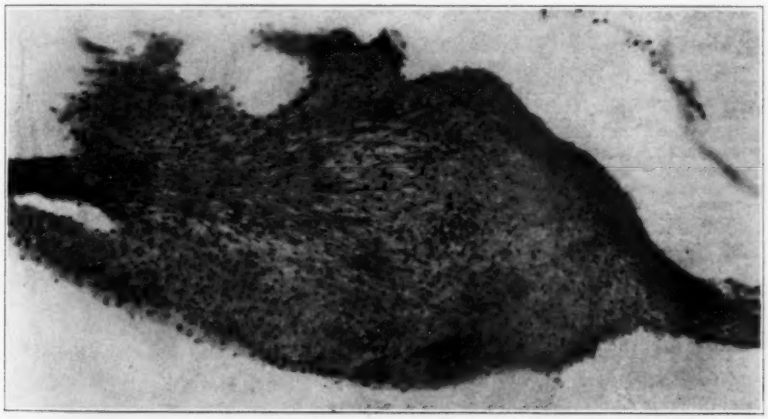

Fig. 3.—Slightly enlarged photomicrograph of the insertion of a tendinous cord into the edge of the tricuspid valve of a rabbit which died twenty-three days after the injection of blood from an endocarditic rabbit. Note the hypertrophy and hyperplasia of the connective tissue and the great proliferation of the endocardium, which has formed granular elements, visible at a glance, on the surface of the valve. Hematoxylin stain.

between the degree of development of the two kinds of lesions and the fact that similar lesions have been observed with great frequency by Miller in cases of spontaneous disease.

The macroscopic and microscopic lesions were always and exclusively confined to the heart; we never found any lesions in the other viscera except lesions of coccidiosis, the presence of which had no relation to the cardiac lesions. The articulations were not involved except for thickening of the reticulohistiocytic layer of the synovial membrane, similar to that occurring in rheumatic arthritis of man and sometimes also in nonendocarditic animals, being without specific character.

BACTERIOLOGIC EXAMINATION

All samples of material injected (e. g., blood, milk and serum) were constantly found sterile when placed in common mediums.

The bacteriologic examination of the heart, circulating blood, principal viscera (liver, kidney and spleen) and articulations of animals affected with endocarditis constantly gave negative results.

Our macroscopic and microscopic anatomic description and our bacteriologic results have been fully confirmed by the control researches that Chini has recently published.

PATHOGENESIS OF THROMBO-ENDOCARDITIS

From the morphologic and bacteriologic features mentioned it appears that we are dealing with a disease that has not yet been described as present in rabbits, either as a spontaneous disease or as one caused by means different from the ones which are likely to produce it through a well known and essentially bacterial action. Although spontaneous endocarditis has never been observed in rabbits, as stated also in Jaffé's [2] recent treatise, it was necessary to ascertain whether our rabbits might not be an exception. Therefore, since in live rabbits it is impossible to detect the existence of endocarditis, which is not revealed even by alterations of nutrition or by diminution of growth, we examined many control animals. For each series of experiments some of the animals from the same breeding farm were employed in the researches, while others, which had undergone no treatment, were examined at once or after a certain lapse of time.

Of this group of controls, 180 were examined; some were examined on their arrival from the breeding farm but most of them after a few months' stay in compartments in which no case of endocarditis had yet appeared, so that they could be considered as not yet infected.

2. Jaffé, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere (Kaninchen, Meerschweinchen, Ratte, Maus), Berlin, Julius Springer, 1931.

Endocarditis was found in only 4 animals; strictly speaking, in 2 cases it should be considered as spontaneous; the other 2 animals were kept for several months in cages that, having been occupied by a number of endocarditic rabbits, could be considered infected, as will be seen from what will be stated later. It follows therefore that endocarditis in the animals we used appeared spontaneously only with extreme rarity.

The same conclusion may be deduced from some other observations: Of 263 rabbits which had undergone the various procedures likely to cause endocarditis and which had died within three weeks after the injection, only 3 showed endocarditic lesions, while of the 441 that lived longer, as many as 163 were endocarditic. This fact, besides having the aforementioned meaning, has enabled us to infer that the time necessary for the appearance of endocarditis exceeds three weeks after the injection.

Lately Chini, one of those who have undertaken the control study of our results, has advanced the suggestion that the incubation time may be even shorter, about four to eight days. We cannot exclude the fact that this may happen also if some conditions affecting the rabbits and the virulence of the hypothetic virus are varied; but in this case these facts, as well as the attempts at transmission, have not yet been demonstrated, since, owing to the particular conditions under which Chini's experiments were made, it is possible that the animals in which endocarditis was noted after a few days were spontaneously affected with the same disease even before the injection was given. Most of the rabbits came from a small breeding place where, as Chini himself demonstrated, the disease occurred spontaneously with great frequency.

Owing to the modalities of the provoking treatments which we carried out, chiefly the injection of sterilized milk, we could reject the hypothesis that the disease in rabbits is to be ascribed to a pathogenic agent contained in the injected material. Therefore only two hypotheses were left for consideration in interpreting the observed facts: (1) that endocarditis might be ascribed to infectious agents preexisting in the animal and activated by the experimental treatment and (2) that the disease might be ascribed directly to the chemical or chemicophysical action of the injected material.

A physical or chemicophysical etiology appeared hardly probable at first sight, because nothing similar has ever been ascertained after such treatments by hundreds of careful research workers; so it was logical to consider the influence of some other factor which perhaps was not common to all the rabbits. Therefore, subsequent researches were made so as to bring into evidence the infectious nature of the disease, which seemed the most probable factor.

In view of this hypothesis the most complete isolation was maintained for the development of further researches, as has been stated in the description of our technical procedure.

The first experiments consisted of injecting whole blood and blood of endocarditic rabbits filtered through an L_3 Chamberland filter, and these yielded widely positive results. Seventy-two of the 118 rabbits were affected with endocarditis (we include here and later only animals which either died or were killed more than three weeks after the injection). However, this type of experiment has no absolute meaning,

TABLE 1.—*Summary of Data* *

Injected Material	Rabbits Which Died More Than 3 Weeks After Injection		Rabbits Which Died Within 3 Weeks After Injection	
	Total No. of Rabbits	No. of Endocarditic Rabbits	Total No. of Rabbits	No. of Endocarditic Rabbits
Blood from patients with rheumatic fever	105	43	35	3
Blood from patients not affected with rheumatic fever	115	21	28	0
Blood from healthy men	5	0	12	0
Blood from endocarditic rabbits	90	54	44	0
Blood filtrate from endocarditic rabbits	28	18	12	0
Blood from healthy rabbits	18	2	16	0
Suspension of endocarditic vegetations	10	4	8	0
Normal sterile horse serum	18	5	22	0
Sterilized unskimmed milk	52	16	28	0
Streptococcus cultures (injected intravenously)	..	..	58	0†
Totals	441	163	263	3

* Of 180 rabbits which received no treatment, 4 appeared to be affected with endocarditis. It should be noted that 2 of these 4 rabbits had been kept a long time (several months) in a compartment that was supposed to be infected.

† The 6 rabbits with polypous endocarditis observed in this group of animals are not mentioned here, because their condition was entirely different from the endocarditis in question. For the description of the morphologic picture, reference should be made to our work entitled "La questione del tropismo elettivo degli streptococchi." [1c]

because the result may be ascribed, in the absence of a virus in the injected material, to the mechanism set in action by the injection of sterile milk. In order to avoid this objection, we attempted to transmit the disease by means of small quantities of material rich in virus, such as the endocarditic vegetations. Four of 10 rabbits showed evident endocarditis after injection into the peritoneal cavity of a suspension in physiologic solution of sodium chloride of the vegetations from two hearts, removed by a perfectly sterile process.

A subsequent series of experiments was carried out in order to ascertain whether the disease, once induced, could be transmitted spontaneously to other animals. We were led to this attempt also by the observation of a few cases of endocarditis in rabbits that had been

kept a long time in compartments and cages in which endocarditic rabbits had previously been kept. For this purpose we inoculated some rabbits with either human blood or milk; then we immediately put 2 inoculated and 2 noninoculated rabbits in each cage. In this manner, allowing for a three week incubation period for the disease after the inoculation, allowing several days for the hypothetic spontaneous spread of the disease from the infected rabbits to the others living in the same cages and estimating the time necessary for the disease to develop in the latter animals as twenty-one days, we could foresee that theoretically the infection could not be manifested until fifty days or more after the experiment was started. In fact, of 19 animals which had not been given injections but which had been kept in a cage with endocarditic rabbits for not less than fifty days, as many as 8 were affected with grave thrombo-endocarditis; while of the 16 that had lived for a shorter

TABLE 2.—*Attempts to Transmit Endocarditis Spontaneously*

	Total No. of Rabbits	Endocarditic Animals
Rabbits which had remained more than 50 days in a cage with endocarditic animals	19	8
Rabbits which had remained less than 50 days in a cage with endocarditic rabbits	16	0

time, none seemed to be diseased. At the same time some other rabbits, although they had been given injections, did not appear to be affected later with endocarditis, and none of several rabbits living in common with them seemed to be diseased.

In this manner we obtained evidence that one of the following conditions is necessary for the appearance of endocarditis: (1) the injection of specified material (for instance, human or rabbit blood, horse serum, milk or suspension of endocarditic vegetations) or (2) prolonged contact with other rabbits affected with endocarditis. The conditions of life, feeding and other features common to all animals had no influence on the appearance of endocarditis.

CONCLUSIONS

On the whole, the described experiments permit the following conclusions:

It is possible to cause a disease not previously described in rabbits—thrombo-endocarditis—which shows rather characteristic clinical and anatomic features.

The means likely to cause the disease consist of an endoperitoneal injection of human or rabbit blood, horse serum or sterile milk. We

have not excluded the possibility that a procedure differing from ours as to manner of introduction or as to the nature of the injected material may not produce the same result. For five years this phenomenon was constantly obtained with remarkable frequency in a number of rabbits coming from different breeding places in the province of Turin.

That an infectious disease was present was demonstrated by the transmission by injection of a minimal quantity of material (suspension of endocarditic vegetations), rather than by anatomic characteristics, and mostly by the evidence of spontaneous infection from one animal to another.

The constant sterility of the blood and viscera of the affected animals enabled us to ascribe the disease to an unknown virus, probably an infravirus. The latter must have been latent in the animals, because the disease was caused also by the injection of sterile material, which evidently made the animals sensitive to the pathogenic action of the virus or directly increased the virulence of the virus.

In our animals the disease was almost always directly dependent on the treatment given, since the occurrence of spontaneous endocarditis was demonstrated as being exceptionally rare in our animals.

It is, however, possible that in other cases the disease may appear spontaneously with greater diffusion when the animals contain a more active virus or are more sensitive to it; which means that in nature conditions might be realized which in our animals were brought into action with technical artifices. This has lately been demonstrated by Chini, who, in studying a large number of animals for several years with negative results, has observed that there is a small breeding place where endocarditis is spontaneous and frequent.

The whole problem reminds us of the problem centered about Miller's number 3 virus. As is well known, this virus was made evident by the injection of blood from persons affected with rheumatic fever into the testicle of a rabbit and by successive rapid transmission from one animal to another, always by way of the testicle, until the appearance of the characteristic orchitis. But in our cases the localization and the character of the lesions, the conditions of transmissibility which revealed the persistence of the virus in each animal for a longer time and the existence of a longer period of incubation demonstrated definitely that Miller's virus was not concerned.

The disease we have described presents a twofold interest: First, the possibility of its appearance after various experimental treatments should be borne in mind by any one undertaking further study of the transmission of infectious diseases, as it may constitute a source of error, especially on account of its anatomic similarity to the lesion of human rheumatic endocarditis, and, secondly, this disease constitutes

a new example of the phenomena of biotropism the study of which, just begun in experiment animals, will probably reveal unhoped for applications to human pathologic conditions.

SUMMARY

We have described a new disease of rabbits, thrombo-endocarditis, which, although occasionally spontaneous, may frequently be caused by various forms of treatment; which may be transmitted from one animal to another either by means of small quantities of infectious material or spontaneously, and which has been ascribed to a virus which is still unknown and is probably infravisible.

PNEUMOCOCCIC ENDOCARDITIS

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Pneumococcic endocarditis is considered a relatively rare condition, although a review of the literature discloses numerous case reports of the disease. Osler,[1] Netter,[2] Preble,[3] Menetrier,[4] Locke[5] and Thayer[6] have reported on series of personally observed patients or on collected reports of cases. In 1927 Goldstein and Goldstein[7] reported 8 cases of pneumococcic infection in which endocarditis was noted post mortem, although the cause of the endocarditis remained in doubt in several instances. Subsequently, other authors[8] have reported isolated cases or small groups of cases of pneumococcic endocarditis, the diagnosis having been made by inference, by bacteriologic methods or by histologic study of the vegetation.

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Dr. Ralph Johansmann, of the Department of Pathology, cooperated in this study.

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The present report is based on a study of 19 patients with pneumococcic endocarditis, 17 of whom were observed by me. While the presentation deals largely with the incidence, predisposing factors, clinical data, methods of treatment and necropsy observations, an attempt is also made to set up bacteriologic and clinical criteria for the prompt diagnosis as well as the treatment of this disease.

The inference should be that acute endocarditis occurring during the course of lobar pneumonia should be considered pneumococcic in origin until proved otherwise. Preble [3] found less than 6 per cent of exceptions to this dictum. On the other hand, Locke [5] found that more than 50 per cent of the cases of acute endocarditis occurring during pneumonia were due to organisms other than the pneumococcus. With improved methods of culture and rapid identification of the pneumococcus, it is believed that these discrepancies will largely disappear. Locke's dogmatic statement, "The final test should always be the actual demonstration of the pneumococcus in the valves," not only is almost impossible of fulfilment but precludes the making of the diagnosis ante mortem. Moreover, the identification of pneumococci in the vegetations must rest on bacteriologic rather than on morphologic evidence. In 10 of the 15 cases in which autopsy was performed, the vegetations were cultured; each time the same pneumococcus was grown which was cultivated from the blood of the patient during life. Lord pointed out the danger of contamination from the blood of bacteremic patients. In addition, the following method was employed, which at least partially obviates the possibility of blood contamination: The heart is preserved in solution of formaldehyde as usual; after varying intervals, portions of the vegetations are removed, washed thoroughly in sterile saline solution, macerated and inoculated into blood broth. This method has yielded pure cultures of pneumococci in vegetations which had remained in preserving solutions as long as twenty-two months; in each instance the pneumococcus was of the same type as that detected in the body during life. This finding is certainly more than a coincidence and lends support to the belief that acute endocarditis occurring during the course of pneumococcic pneumonia with bacteremia is due to the pneumococcus rather than to some other organism. As further evidence that these endocarditides are due to the pneumococcus, gram-positive lanceolate diplococci were demonstrated in the vegetations histologically.

In view of the fact that there are potent serums available against several types of pneumococci, it seems timely to set forth certain criteria which enable the diagnosis to be made and treatment to be instituted. The persistent presence or the recurrence of pneumococcemia is presumptive evidence of a purulent focus and is indispensable in substantiating the diagnosis of endocarditis. This alone, however, is not sufficient. Embolic phenomena occurring in patients with pneumo-

coccemia are strongly presumptive evidence of endocardial damage. The appearance of signs of valvular incompetence during diastole in the presence of bacteremia may be safely referred to endocarditis (Preble). Thayer also said he considered such signs as confirmatory. Systolic murmurs must be evaluated much more carefully, for obvious reasons; the sudden appearance and persistence of such a murmur should, however, arouse suspicion of organic change. These signs may not be present in every case; in fact, the application of these criteria permitted diagnosis of endocarditis in only 10 of the 19 cases reported. Nevertheless, such criteria did not lead to a mistaken diagnosis in a single instance.

During the twenty-three month period from Oct. 1, 1935, to Sept. 1, 1937, 655 patients were admitted to the medical service of the Cincinnati General Hospital with acute pneumococcic infection. The latter term is used in preference to pneumonia, for in a few instances it was impossible to ascertain whether the endocarditis had preceded or whether it had been a sequel of pneumonia; in others, bacteremia was known to have existed longer than the necropsy indicated the pneumonic lesions had been present. In this series of 655 patients the diagnosis of acute endocarditis was made in 19 instances, either clinically or by pathologic and bacteriologic methods. Thus in this series the incidence of endocarditis in acute pneumococcic infection was 2.9 per cent. In the literature the incidence has been reported as varying from 0.06 to 2 per cent. In 104 of the 214 fatal cases necropsy was performed, and in 15 cases (14.6 per cent) acute endocarditis was observed. This incidence is much higher than that recorded by any author except Osler,[1] who reported 16 in 103 necropsies. Wherever clinical and necropsy incidences are recorded, there is a great discrepancy in the figures, as noted in the present series, and the impression cannot be escaped that pneumococcic endocarditis is considerably more common than is usually supposed.

A consideration of the relative frequency of the etiologic agents of bacterial endocarditis tends also to show that the importance of the pneumococcus may have been underestimated. During the same twenty-three month period 46 necropsies revealed acute or subacute vegetations on one or more valves, and in 15 cases the vegetations were proved to be due to the pneumococcus. There was an additional instance of acute vegetative endocarditis, the patient dying of purulent meningitis (gram-positive diplococci) and empyema, but it is not included in this series because no bacteriologic studies were made.

PREDISPOSING FACTORS

Sex does not appear to have any importance as a predisposing cause. In this series there were 14 males (73.8 per cent) and 5 females (26.2

per cent). This ratio prevailed almost exactly for the whole group of patients with acute pneumococcic infection, the figures being 72.3 and 27.7 per cent, respectively.

Likewise, race does not seem to be a factor. Fifty per cent of the cases of acute pneumococcic infection occurred in the Negro race, and the mortality percentage of white and Negro patients did not vary appreciably. Ten of this series of patients with endocarditis were white, and 9 were Negroes.

Pneumococcic endocarditis may occur at any age. It is, however, primarily a disease of middle and later adult life. Whereas more than half the patients with acute pneumococcic infection were of the age group from 11 to 40, patients under 13 not being admitted to the medical service, 80 per cent of the patients with endocarditis were over 40. However, patients in the fifth and sixth decades comprised a preponderance of the series. This is in marked contrast to subacute bacterial endocarditis, which shows a predilection for the younger age groups.

The apparent increase in the incidence of this complication may raise the question of serum therapy as a predisposing cause. Eight of the infections were caused by types of pneumococci for which therapeutic serum was not available. In only 5 of the remaining 11 cases was serum given. Consequently, it is doubtful if serum therapy is a predisposing factor in the causation of this disease.

Since Wadsworth [9] first called attention to the occurrence of pneumococcic endocarditis in horses, the opinion has been expressed that the type I pneumococcus was chiefly concerned in producing this complication. In this series several types of organisms occurred relatively more frequently than type I pneumococcus (table 1). This is in accord with the findings of Finland and his associates [10] who found pneumococci of type II and type V to be the more frequent, relatively and absolutely, in a large series of necropsies. Since Bullowa and Wilcox [11] have shown that pneumococci of type II, type III and type V of the commoner types are more likely to invade the blood stream than those of type I, it seems unreasonable to adhere to the belief that those of type I are primarily responsible for the production of endocarditis, especially in view of clinical evidence to the contrary.

Preexisting disease of the valvular endocardium apparently has little influence as a predetermining factor in pneumococcic endocarditis. In

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this entire series of 19 patients, valvular incompetence due to an antecedent infection was diagnosed only once, although 2 other patients had a history of rheumatic symptoms. Four of the patients had serologic evidence of syphilis, but none had signs of syphilitic aortitis or valvulitis.

As a rule the portal of entry of the pneumococcus is reasonably clear. In 15 of the cases the endocarditis followed frank lobar pneumonia while the patient was under observation, or there was a history typical of that disease. Case 4 probably represented a case of invasion from the urethra, although cultures were not made previous to the onset. Bacteremia developed in case 9 after cholecystogastrostomy for obstruction of the common duct. In 1 patient (case 11) fever developed suddenly while he was staying in the hospital to regain cardiac compensation, and he died three days later. In another case (case 3) the onset was insidious, the only complaint being of a sore knee, which represented a purulent metastatic focus of the infecting organism.

CLINICAL COURSE

Pneumococcic endocarditis may complicate pneumonia at any stage of the illness or may occur independent of the disease days or weeks after an apparently uneventful convalescence. If the endocarditis merges with the acute pulmonary infection in regard to time of appearance, it is likely not to be diagnosed. As a rule the onset is rather acute. Six of the patients were afebrile for from two to seven days, when the complication was heralded by a sudden chill with subsequent fever. All but 3 (84 per cent) of this group of patients had chills or chilly sensations, separate and distinct from such symptoms occurring in the early stages of lobar pneumonia, during the course of illness that were directly referable to the endocarditis. The fever was sustained in 12 of the 19 cases; the temperature ranged between 103 and 105 F. (rectal). Four patients showed an intermittent type of fever, although the afebrile periods were of short duration. Three patients had paroxysms of fever with chills, the maximum temperature reaching 108 F. One patient, observed for only three days, was afebrile during the first two days. In only 1 case was the fever moderate, the temperature being sustained between 101 and 102 F.

The pulse rate was invariably accelerated. However, the instability as to rate and volume rather than the actual rate was the outstanding characteristic of the pulse.

As a rule evidence of toxemia was marked. This was especially striking since there were not always signs localizing the infection.

Acute pneumococcic infections of the endocardium caused few subjective cardiac symptoms, as might be expected. In fact, frequently there

were no objective signs. Nine of the patients in this series showed no cardiac murmurs; diastolic murmurs developed in 7 while they were under observation, and the remaining 3 had valvular murmurs on admission to the hospital. One of these 3 patients had been under observation for several years and was thought to have had double mitral and aortic lesions of rheumatic origin; no change was detected in the quality of the murmurs, despite an acute bacterial engraftment on both valves.

The size and shape of the cardiac dulness were usually within normal limits. One patient showed an enlargement which was not explainable by a history of antecedent cardiac disorder or of a long-standing illness.

Abnormalities of rhythm were infrequent. It has been a clinical dictum for many years that fibrillation spares a patient from bacterial endocarditis. One patient (case 14) presented this coincidence, although it could not be ascertained whether or not the obtunded rhythm preceded the onset of the pneumonia. Another patient showed gallop rhythm terminally.

Petechiae were observed in only 5 patients (26.3 per cent). This is in striking contrast to the incidence of petechiae in endocarditis due to Streptococcus viridans. If petechiae are of embolic origin, the relative infrequency of this observation is all the more significant because embolic phenomena in viscera were noted regularly at necropsy. Clinically, two cerebral embolisms and one femoral embolism were observed.

Only 1 patient in this whole series had jaundice, and the jaundice in this instance, due to obstruction of the common duct, was present many months before there was evidence of endocarditis. It is surprising that whereas jaundice is seen in 5 to 10 per cent of the patients with pneumonia, it is rarely recorded as a complication of endocarditis.

Clubbing of the fingers or toes was not noted in this series. In view of the acuteness of pneumococcic endocarditis, it does not seem remarkable that acropachy is seldom observed as an accompanying sign.

A palpable spleen, observed so frequently in subacute bacterial endocarditis, was never recorded in the series. It is not improbable that an enlarged spleen is frequently overlooked because of the patient's acutely ill condition.

Pyarthrosis occurred in 2 patients (10.5 per cent). This finding also may conceivably be overlooked in a very ill patient. In both cases the knee joint was involved; in 1 case a shoulder joint also contained pus. As might be expected, the organism within the joint was of the same type as the one in the endocardial vegetation.

ACCESSORY EXAMINATIONS

Culture of the blood is the most important and indispensable method of confirming the diagnosis of pneumococcic endocarditis. Blood cultures were made for every patient. Only 2 failed to show growth, these

TABLE 1.—*Sum-*

Case	Sex	Race	Age	Hospital Residence	Bacteriologic Data			Other Data
					Sputum	Blood	Vegetation	
1	M	N	21	12/14/35-1/1/36	12/18-VI	12/28-VI	.....	Spinal fluid, 12/29-VI
2	M	W	69	1/4/36-1/30/36	1/6-I	1/20-I 1/22-I	5/11/37-I 12/11/37-I	.....
3	F	N	90	12/8/36-12/11/36	12/10-XI 12/11-XI	12/8-XI (77) 12/11-XI	.....	Spinal fluid, 12/10-XI; fluid from knee joint, 12/9-XI
4	M	N	47	12/31/36-1/3/37	.....	12/31-XX 1/1-XX (134)	.....	Spinal fluid, 12/31-XX
5	M	N	23	1/5/37-2/13/37	1/5-I	1/5-I (500) 1/12-neg.	5/11/37-I	Pleural fluid, 1/14-I
6	F	W	16	1/8/37-1/9/37	1/8-XXIX	1/8-neg.	1/9-XXIX	.....
7	F	W	46	1/10/37-1/12/37	1/10-II	1/10-II 1/12-II	.....	Pericardial fluid, 1/12-II; spinal fluid, 1/12-II
8	M	W	50	2/10/37-3/5/37	2/10-V	2/10-neg. 2/11-neg. 2/16-neg. 2/23-neg. 2/27-V 3/1-V 3/3-V (25)	3/5-V 5/11-V	Spinal fluid, 3/5-V
9	M	W	51	2/15/37-2/25/37	.....	2/19-IX 2/20-IX (24) 2/22-IX	5/11-IX	.....
10	M	W	46	3/24/37-3/28/37	3/26-VIII ‡	3/26-V 3/27-V (800)	.....	Spinal fluid, 3/26-V
11	F	W	60	4/26/37-5/9/37	5/6-VIII 5/7-VIII	5/7-VIII (4,800) 5/8-VIII (440) 5/9-VIII (2)	5/9-VIII	Spinal fluid, 5/9-VIII
12	M	N	40	5/3/37	5/3-IV ‡	5/3-neg.	5/10-IV 5/11-IV	Spinal fluid, 5/3-IV
13	M	N	47	4/5/37-4/30/37	4/5-VII 4/6-VII	4/5-VII 4/6-neg. 4/7-neg. 4/8-VII (36) 4/12-neg. 4/17-VII (4) 4/18-neg. 4/19-VII (2) 4/20-VII (23) 4/22-VII (35) 4/24-VII (25) 4/26-VII (1,500) 4/28-VII (560)	5/1-VII	Spinal fluid, 4/19-neg.; 4/20-neg.; 4/22-VII; 4/29-VII
14	M	N	56	5/18/37-5/19/37	5/18-IV	5/18-IV (16,880) 5/19-IV (15,000)	.....	.....
15	M	N	46	8/10/37-8/18/37	8/10-VIII	8/10-VIII (1,600) 8/11-VIII (320) 8/12-VIII (60) 8/13-VIII (800) 8/14-VIII (300) 8/15-VIII 8/16-VIII (408)	8/18-VIII 9/9-VIII	Pleural fluid, 8/10-VIII; 8/11-VIII
16	F	W	41	1/8/37-1/25/37	1/8-V	1/8-V 1/11-neg. 1/19-neg. 1/21-V (25) 1/23-V	.....	Pleural fluid, 1/19-V
17	M	N	70	2/20/37-3/2/37	2/21-XII	2/21-XII 2/22-XII (160) 2/23-XII (35) 2/24-XII 2/25-neg. 2/26-neg. 3/1-XII	.....	.....
18	M	W	41	3/2/37-3/12/37	3/2-V 3/3-V 3/5-V	3/2-V (490) 3/3-V (450) 3/5-V (60) 3/6-V (115) 3/8-V (88) 3/9-V (356) 3/10-V 3/11-V (350)	.....	Fluid from knee joint, 3/10-V; from shoulder joint, 3/10-V
19	M	W	55	3/25/37-3/31/37	.....	3/26-V (15) 3/29-V (25) 3/30-V (5)	.....	Spinal fluid, 3/30-V

* The roman numerals indicate the type of pneumococci found. The numbers in parentheses refer to the number of colonies per cubic centimeter.

† The Wassermann or Kahn test gave a positive reaction.

‡ Culture of material obtained by swabbing the throat.

mary of Data *

Clinical Data			Necropsy Observations		
Leukocytes	Cardiac Murmurs	Embolic Phenomena	Endocardial Vegetations	Pneumonia	Other Data
12,200	†	.....	Aortic	Lobar and lobular	Meningitis; perivascular scars in myocardium (rheumatic ?)
16,000-20,000	Systolic and diastolic over base, 1/20	Petechiae	Aortic	Lobular	Myocardial degeneration
11,100	Systolic at apex	.....	Mitral	Lobular	Meningitis; pyarthrosis; metastatic abscess and acute infarction of kidney
19,000-26,000	Systolic at apex†	Hemiplegia	Mitral	Lobular	Meningitis; cerebral infarction and abscesses; splenic abscesses; syphilitic aortitis
15,000-49,000	†	.....	Aortic	Lobar	Purulent pericarditis; empyema; mycotic aneurysm of aorta; syphilitic aortitis
20,200	.....	Petechiae	Mitral and aortic	Lobar and lobular	Meningitis; abscess of spinal cord and myocardium; pulmonary embolism
9,000-10,000	.....	Petechiae	Aortic	Lobar and lobular	Meningitis; purulent pericarditis; empyema; myocardial degeneration and fibrosis
13,000-48,000	Diastolic over base, 2/23	Hemiplegia	Aortic and tricuspid	Organizing lobar	Meningitis; fibrinopurulent pleuritis; pulmonary infarction; mural thrombosis; acute diffuse glomerulonephritis
8,000-14,000	.....	Petechiae; femoral embolism	Mitral	Lobar	Meningitis; splenic and renal embolisms; myocardial abscesses; rheumatic scar of mitral valve; adenocarcinoma of ampulla of Vater
12,600	.....	Petechiae	Mitral	Lobar and lobular	Meningitis; panophthalmitis; renal and splenic infarcts
9,000-16,000	Aortic diastolic, apical systolic and diastolic before entry	.....	Mitral, aortic and about foramen ovale	Lobular	Meningitis; pulmonary infarctions; healed rheumatic endocarditis of mitral and aortic valves; pyelonephritis
17,000	.....	.....	Aortic	Resolving lobar	Meningitis; focal embolic nephritis
5,000-23,000	Systolic and diastolic, loudest at apex, 4/29	.....	Aortic	Resolving lobar	Meningitis; miliary abscess of kidney; acute focal myocarditis; myocardial fibrosis
7,000-8,300	†	.....	Aortic	Lobar	Syphilitic aortitis; acute pyelonephritis
14,000-35,000	.....	.....	Tricuspid	Lobular	Empyema
15,000-17,000	Systolic and diastolic over base and apical systolic, 1/19	.....	No necropsy; clinical diagnosis of lobar pneumonia followed by empyema and acute aortic valvulitis		
.....	Diastolic over base, 2/28	.....	No necropsy; clinical signs of lobar pneumonia; signs of aortic regurgitation appeared one week after entry		
6,000-17,000	Diastolic over base, 3/6	.....	No necropsy; clinical diagnosis of lobar pneumonia which began to resolve; pyarthrosis developed after signs of aortic regurgitation appeared		
9,000-10,000	Diastolic over base, 3/28	.....	No necropsy; clinical diagnosis of unresolved lobar pneumonia; meningitis followed signs of aortic regurgitation		

patients having died after a few hours in the hospital, and the etiologic factor was proved by culture from the valves at necropsy. Colony counts were made for all blood cultures. The number of colonies had no prognostic significance. The highest count exceeded 16,000 colonies per cubic centimeter. The type specificity of the organisms was always striking. In other words, examination of the sputum, joint fluid, empyema pus or cerebrospinal fluid or culture material from the lung (by suction) and throat almost invariably disclosed a pneumococcus of the same type as the organism found in the blood stream or in the vegetation. A single exception occurred in case 10, in which type VIII pneumococci were found in a single culture of material from the throat, whereas several blood cultures and the cerebrospinal fluid showed type V pneumococci.

An examination of the various components of the blood usually disclosed important deviations from the normal, but there was no typical pattern. As a rule leukocytosis was present, as in other pneumococcic infections, although this was not always striking. Two patients had white blood cell counts of 10,000 or less. The great majority showed counts between 10,000 and 20,000; six counts were in excess of 20,000, the highest being 48,000. There was no apparent correlation between the number of circulating leukocytes and the clinical data; it may be significant, however, that the patient with the lowest count (8,300) had overwhelming bacteremia (15,000 colonies or more per cubic centimeter). There was invariably associated with the leukocytosis a relative increase in the number of polymorphonuclear neutrophils. Anemia of the hypochromic type was present in about half the cases. This became apparent in those cases in which the disorder was of longer duration, as might be expected. Urinary findings were those of an acute febrile illness. Albuminuria was noted in half the patients. Despite microscopic and gross evidence of infarction at necropsy, hematuria was not observed in any cases. White blood cells and casts were found occasionally.

Electrocardiographic tracings were made for 5 patients. One showed a normal tracing, despite clinical signs of acute aortic insufficiency. The others were interpreted as indicative of myocardial disease of varying degree. One tracing (case 11) showed a PR interval of 0.22 second, although the interval two months previously had been 0.16 second. White [12] recorded this as an infrequent finding in acute bacterial endocarditis. Segal [13] also found this to be more commonly observed in

12. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

13. Segal, M. S.: Bacterial Endocarditis with Special Reference to Cardiac Irregularities: Clinical and Pathological Study of One Hundred and Ninety-One Cases, Am. Heart J. **11**:309, 1936.

cases of involvement of the aortic valve than in cases of mitral involvement.

Pneumococcic endocarditis in our experience usually pursued an acute and rapid course. Obviously, it is practically impossible to ascertain the exact date of onset. In 17 of the 19 cases the disorder terminated within five weeks of the onset of the acute pneumococcic infection, of which the endocarditis was presumably a complication or sequel. One patient gave a history of lobar pneumonia at least five months previous to entry, with uneventful convalescence; then there was a gradually increasing feeling of malaise, interrupted suddenly by chills and fever. Judging from clinical data, the estimated duration of the process exceeded two weeks in only 1 instance. Fortunately it was

TABLE 2.—*Types of Pneumococci in Nineteen Cases of Pneumococcic Endocarditis*

Type	Incidence	Type	Incidence
I	2	VIII	2
II	1	IX	1
IV	2	XI	1
V	5	XII	1
VI	1	XX	1
VII	1	XXIX	1

TABLE 3.—*Necropsy Data for Patients with Pneumococcic Endocarditis*

Involvement	No. of Cases	Involvement	No. of Cases
Aortic	7	Left side of heart	13
Mitral	4	Right side of heart	1
Tricuspid	1	Both sides of heart	1
Aortic and mitral	2		
Aortic and tricuspid	1		

possible to observe 5 patients throughout the primary and secondary phases of the infection; cultures were made at frequent intervals after spontaneous or induced defervescence of the fever; in 1 instance the blood culture again gave positive results fourteen days before death. The actual duration of the endocarditis probably is greater than the period indicated by pneumococcemia but less than the total period of the illness.

The disease terminated in meningitis in 13 (68.4 per cent) of the cases. Only 1 of the 6 remaining patients failed on postmortem study of the calvarium or of the spinal fluid to show evidence of meningitis. This patient also was the only one to show purely right-sided endocarditis; consequently, the incidence of meningitis may well have been higher, especially since there was such a preponderance of left-sided cardiac lesions.

PATHOLOGIC OBSERVATIONS

The vegetations of pneumococcic endocarditis vary considerably in size, color and distribution. The great majority of the vegetations show ulceration, either grossly or microscopically; case 13 demonstrated ulceration which progressed to actual rupture of the valve. The vegetations vary in size from papilliform or cauliflower-like masses, 1.5 cm. in diameter, to mere excrescences of the endothelium. They are usually friable. They are grayish red, or sometimes there is a mottling of red and gray. The distribution of lesions in this disease is shown in table 1. Sometimes the pneumococcus attacks the endocardium elsewhere, leaving the valves intact. In case 11 there were vegetations around the foramen ovale in addition to those on the valves. The predilection of the pneumococcus for the left side of the heart is not surprising, since in the great majority of instances the portal of entry is probably the lung. The site of election is shown in the table. The incidence of involvement of the aortic valve is striking; no plausible reason is apparent, although Netter, Preble and Thayer found a similar election. Lesions on the pulmonary valve, infrequently seen in any type of endocarditis, were not observed, although such lesions have been reported.

The immediate effects of the endocarditis on the heart itself were difficult, if not impossible, to determine. There was moderate hypertrophy of the myocardium in more than two thirds of the cases in which necropsy was performed, but coexistent cardiovascular disease precluded any conclusion concerning the cause. It may be significant, however, that the largest heart (case 15), weighing 700 Gm., was that of a patient with little evidence of other disease yet showing pure tricuspid endocarditis with dilatation of the ring. Mural thrombi were present in only 3 instances. One vegetation eroded the aortic intima to form a small mycotic aneurysm.

Pneumonia was present in all the 15 cases in which necropsy was performed. It was lobar in 6, lobular in 5 and mixed in 4. In only 2 was there evidence of resolution; in 1 case organization was taking place. In case 11 the pneumonia probably was entirely secondary to infarction.

While pneumococcic infections are notoriously prone to cause purulent foci, the incidence of such suppurative processes was striking in this group of cases. Only 2 of the 15 patients failed to reveal such foci; and in neither of these cases was complete necropsy performed. Although meningitis occurred most frequently, a multiplicity of purulent focal processes was seen in more than 50 per cent of the cases at necropsy. These foci included empyema of the pleural cavity, pericarditis, pyarthrosis, abscesses of the myocardium, abscess of the brain, abscess of the spinal cord and focal embolic nephritis.

Although the spleen was never palpated clinically, it was almost invariably enlarged at necropsy. Usually it appeared as a moderately enlarged organ with a friable pultaceous pulp; occasionally follicular markings were lost.

THERAPY

In view of the fact that pneumococcic endocarditis is invariably reported as a disease of hopeless prognosis, discussion of modes of therapy may seem futile. However, Wadsworth,[9] after observations of the process in horses, said he was confident that he saw scars of old healed inflammations of the valves, the implication being that they were due to the pneumococcus. If one may make an analogy between this type and other types of acute bacterial endocarditis,[14] it is not unreasonable to suspect that at least a small percentage of patients recover. Preble [8] reported on 4 patients, including 2 of his own, who recovered; 1 of them presented all the findings for an antemortem diagnosis and must certainly be considered as representing a case of genuine pneumococcic endocarditis. Lanbry and Coffin [15] reported the only other instance of recovery since Preble's report, but here the diagnosis is by no means so convincing. The authors treated their patients with antipneumococcus serum and later with vaccine. Immunologic studies were not made of the patients of this series, but the rationale of serum and vaccine therapy does not seem well founded. Wadsworth demonstrated acute active vegetations in horses which were producing potent therapeutic serum. Three of the patients of the present series (cases 5, 13 and 16) received sufficient serum to sterilize the blood stream temporarily, yet they subsequently had endocarditis. Horder [16] reported the employment of diathermy without encouraging results. He also reported the use of roentgen therapy with success in 1 case. One of the patients in the present series (case 18) was given high voltage roentgen therapy over the precordium, with no apparent effect on the course. Since there is some evidence that certain strains of pneumococci may have a thermal death point compatible with the maintenance of human life, 1 patient (case 8) was treated by hypertherm exposures. This treatment did not prove successful; the cooperation was poor and the program was not carried to its completion. Another patient (case 15) was treated with sulfanilamide; he was given the drug for seven days in large doses, although

14. Perry, M. W.: Gonorrheal Endocarditis with Recovery: A Case Report, Am. J. M. Sc. **179**:599, 1930; Further Note on a Case of Gonorrheal Endocarditis with Recovery, ibid. **185**:394, 1933. Hamman, L.: Healed Bacterial Endocarditis, Ann. Int. Med. **11**:175, 1937.

15. Lambry, C., and Coffin, M.: Endocarditis infectieuse primitive a pneumocoques terminée par la guérison, Bull. et mém. Soc. méd. d. hôp. de Paris **52**:281, 1928.

16. Horder: Septic Endocarditis, Lancet **2**:174, 1936.

the concentration in the blood did not exceed 8 mg. per hundred cubic centimeters until the day before death, when it was 17 mg. Far from sterilizing the blood stream, it actually did not change the colony count appreciably. As it was found that solution of formaldehyde and other preservatives failed to kill the pneumococcus embedded in vegetations post mortem, it scarcely seems likely that a nonspecific drug, so innocuous to tissue as sulfanilamide, would effect the desired result.

In conclusion, the problem of mode of therapy seems to be frankly one of prevention. Others have also been unimpressed by serum or drug therapy. Wadsworth's finding that horses may produce potent therapeutic serum yet may have endocarditis is discouraging to the prospects of serum therapy. However, that should not be a contraindication to large doses of specific serum when the diagnosis is once made. Since endocarditis has its origin in bacterial invasion of the blood stream and since potent therapeutic serums are today available, prompt and vigorous serum treatment of acute pneumococcic infection should be instituted. In addition to serum therapy, surgical eradication or at least surgical drainage of accessible purulent foci should be employed without hesitance, for such foci constitute a constant potential source for invasion of the blood stream. Those two methods of attack on acute pneumococcic infection should do much to decrease the incidence of this complication markedly.

CONCLUSIONS

Acute endocarditis occurring in the course of pneumococcemia is probably always due to the pneumococcus.

Acute endocarditis is a considerably more frequent complication of pneumococcic sepsis than is generally believed.

Pneumococcic endocarditis may be diagnosed ante mortem in about 50 per cent of the cases if certain laboratory facilities are available.

Pneumococcic endocarditis usually occurs as a complication or sequel of pneumococcic pneumonia, runs an acute course, attacks especially the valves of the left side of the heart, is characterized by embolic phenomena and terminates in the majority of instances in purulent meningitis.

As serum and drug therapy of pneumococcic endocarditis has been almost uniformly unsuccessful, therapeusis should be largely prophylactic, namely, the prevention of bacteremia by means of potent specific serum and the removal or drainage of purulent foci.

PRIMARY BENIGN TUMOR OF THE HEART OF FORTY-THREE YEARS' DURATION

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Tumors of the heart are rare. A large series of autopsy reports (approximately 40,000 cases) show that metastatic growths in the heart occur in approximately 0.5 per cent of cases, whereas primary tumors are found in 0.03 per cent (Yater [1] and Mead [2]). On the other hand, studies of cases of malignant growth with disseminated metastases reveal an incidence of about 7.5 per cent in cases of cardiac involvement (Yater,[1] Burke [3]). Metastatic tumors have been reported as diagnosed during life in only 10 cases, the first by Roesler,[4] in 1924, and all the others since 1930 (Heninger,[5] Willius and Amberg,[6] Fishberg,[7] Schnitker and Bailey,[8] Doane and Solis-Cohen,[9] Smith [10]). Such tumors may involve any part of the heart, but especially the right auricle. They have been described as arising from almost any type of malignant tumor anywhere in the body. Usually they produce no symptoms and are found accidentally at autopsy. Symptoms or signs of cardiac involvement in a case of known malignant involvement may

1. Yater, W. M.: Tumors of the Heart and Pericardium, Arch. Int. Med. **48**: 627 (Oct.) 1931.

2. Mead, C. H.: Metastatic Carcinoma of the Heart, Secondary to Primary Carcinoma of the Lung, J. Thoracic Surg. **2**:87, 1932.

3. Burke, E. M.: Metastatic Tumors of the Heart, Am. J. Cancer **20**:33, 1934.

4. Roesler, O. A.: Vier seltenere Herzbefunde: Ein Beitrag zur Herzdiagnostik, Zentralbl. f. Herz- u. Gefässkr. **16**:261, 1924.

5. Heninger, B. R.: Clinical Aspects of Pericardial Metastasis, Ann. Int. Med. **7**:1359, 1934.

6. Willius, F. A., and Amberg, S.: Two Cases of Secondary Tumor of the Heart in Children, in One of Whom the Diagnosis Was Made During Life, M. Clin. North America **13**:1307, 1930.

7. Fishberg, A. M.: Auricular Fibrillation and Flutter in Metastatic Growths of Right Auricle, Am. J. M. Sc. **180**:629, 1930.

8. Schnitker, M. A., and Bailey, O. T.: Metastatic Tumor of the Heart: A Case Diagnosed During Life, J. A. M. A. **108**:1787 (May 22) 1937.

9. Doane, J. C., and Solis-Cohen, L.: Symmetrical Adrenal Neuroblastoma Metastasizing to the Right Auricle, J. A. M. A. **109**:578 (Aug. 21) 1937.

10. Smith, D. S.: Neoplastic Involvement of the Heart, J. A. M. A. **109**:1192 (Oct. 9) 1937.

suggest an antemortem diagnosis. The cardiac disturbances most commonly noted have been arrhythmias, bloody pericardial effusion, localized edema in the face, neck or hands, excessive dyspnea, oppression in the chest, and the acute onset of signs of congestive heart failure. Naturally, the symptoms and signs depend on the size and the location of the tumor.

Primary tumor of the heart may be either malignant or benign. Only 2 cases have been reported in which the diagnosis was made before death; in both the tumor was malignant. The first case was reported by Barnes, Beaver and Snell,[11] in 1934. Their patient, a woman aged 62, with symptoms and signs of acute pericarditis, had pain in the region of the deltoid muscle. Biopsy revealed the cells of a malignant tumor, and later an electrocardiogram disclosed complete auriculoventricular dissociation. Autopsy showed rhabdomyosarcoma of the right auricle, pericardium and right ventricle.

In the case reported by Shelburne,[12] in 1935, the diagnosis was made on the basis of finding a bloody pericardial exudate in a patient who showed no fever or signs of tuberculosis. The electrocardiogram showed partial bundle branch block. Four days later there were signs of acute cardiac decompensation. At autopsy, sarcoma of the pericardium was demonstrated.

Recently, Shelburne, as well as other authors,[13] have erroneously quoted Goettel[14] as having credited Pavlowski[15] with reporting the only benign tumor of the heart ever diagnosed before death. Actually Pavlowski[16] reported a case of myxoma of the left auricle in which autopsy was performed. Like other authors who have reported cases of primary tumor of the heart, he reasoned backward from the autopsy protocol and showed how and why the symptoms were produced. His own antemortem diagnosis was *dilatatio cordis* due to a chronic char-

11. Barnes, A. B.; Beaver, D. C., and Snell, A. M.: Primary Sarcoma of the Heart: Report of a Case with Electrocardiographic and Pathological Studies, Am. Heart J. **9**:480, 1934.

12. Shelburne, S. A.: Primary Tumors of the Heart, with Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death, Ann. Int. Med. **9**:340, 1935.

13. Gilchrist, A. R., and Miller, W. G.: Paroxysmal Auricular Tachycardia Associated with a Primary Cardiac Tumor, Edinburgh M. J. **43**:243, 1936. Yater.[1] Mead.[2] Schnitker and Bailey.[8]

14. Goettel, L.: Ein Fall von primären Herztumor, Deutsche med. Wchnschr. **45**:937, 1919.

15. Pavlowski, R. A.: Ueber Herzthromben: Gestielte Thromben oder "wahre Polypen" des Herzens, Ztschr. f. klin. Med. **26**:482, 1894.

16. Pavlowski, R.: Beitrag zum Studien der Symptomatologie der Neubildungen des Herzens. Polypose Neubildungen des linken Vorhofs, Berl. klin. Wchnschr. **32**:393, 1895.

acteristic cause. Where it was and of what nature could not be determined. He stated that it was something out of the ordinary.

A primary tumor may occur in any portion of the heart. The rarest location is on the valves. Such a tumor is usually small and of no clinical significance (Ferel [17]). The most frequent site of a primary tumor is the left auricle, in contrast to a metastatic tumor, which most often invades the right auricle. However, a tumor may be present in the wall of any of the cardiac chambers (Karrenstein [18]) and may occur at almost any age. In children rhabdomyoma occurs with tuberous sclerosis and with other signs of congenital defects (Fiddler [19]). The first rhabdomyoma in an adult was reported in 1928 by Bradley and Maxwell.[20] A tumor may be present without any cardiac manifestations, and if symptoms or signs occur they depend, as has been remarked, on the size and the location of the tumor. One of the most interesting tumors described in the literature is the pedunculated myxoma of the left auricle which drops into the auriculoventricular opening and intermittently occludes the mitral valve (Pavlowski,[16] and Houck and Bennett [21]). In other cases the conduction system is involved, and arrhythmia occurs (Wegman and Egbert [22]).

All primary tumors of the heart are of mesoblastic origin—fibroma, myxoma, sarcoma, rhabdomyoma. In much of the earlier literature one finds a discussion of the differentiation between cardiac thrombi and myxomas; some of the earlier so-called tumors were actually thrombi (Chiari [23] and Lymburner [24]). With the better technical facilities available for microscopic study in recent years, there is no real difficulty today in differentiating between these two conditions.

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17. Ferel, F. C.: Two Cases of Primary Neoplasm of the Cardiac Valves, Internat. Clin. **4**:147, 1919.

18. Karrenstein: Ein Fall von Fibroclastimyxom des Herzens und Kasuistiches zur Frage der Herzgeschwülste, besonders der Myxome, Virchows Arch. f. path. Anat. **194**:127, 1908.

19. Fiddler, R. S.; Kissane, R. W., and Koons, R.: Primary Fibrosarcoma of the Heart, Am. Heart J. **13**:736, 1937.

20. Bradley, E. B., and Maxwell, E. S.: Primary Neoplasms of the Heart: Report of an Unusual Case, J. A. M. A. **91**:1352 (Nov. 3) 1928.

21. Houck, G. H., and Bennett, G. A.: Polypoid Fibroma of the Left Auricle (So-Called Cardiac Myxoma) Causing a Ball-Valve Action, Am. Heart J. **5**:787, 1930.

22. Wegman, M. E., and Egbert, D. S.: Congenital Rhabdomyoma Associated with Arrhythmia, J. Pediat. **6**:818, 1935.

23. Chiari, H.: Myxom des rechten Vorhofs: Ploetzlicher Tod durch Geschwulstembolie der Lungenschlagader, Centralbl. f. allg. Path. u. path. Anat. **52**:291, 1931.

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As for the clinical history and the intra vitam diagnosis of cardiac tumors, it must be admitted that practically all the information so far published has been based on ex post facto reasoning. Meroz [25] reviewed the subject in 1917, attempting to show from a casuistic analysis of some cases how the diagnosis should be made. Yet the first metastatic malignant tumor of the heart was diagnosed in 1924 (Roesler [4]) and the first primary malignant tumor in 1934 (Barnes, Beaver and Snell [11]); as yet no benign primary tumor has been diagnosed during life. Siegel and Young [26] studied the electrocardiographic changes in all cases of cardiac tumor reported up to 1933 and concluded that there was great similarity of the electrocardiographic findings in cases of tumor of the heart and in myocardial changes from other causes, especially coronary disease. Minor differences were noted, especially the lack of reciprocal direction of the T wave in leads I and III and the failure to show deviation from the isoelectric level in the ST segment. They also suggested that the electrocardiographic changes in cases of tumor gave some evidence as to the location of the neoplasm in the heart. These findings certainly are not specific.

REPORT OF A CASE

The patient was born in 1872 and died on Dec. 7, 1935. Friends of his youth stated that although he led an active life for his first twenty years, "he had to be careful of his health." There was no history of rheumatism or of infection. Apparently during his youth he was not seriously incapacitated, and in his late teens he was accepted for the only life insurance policy he ever obtained. He had a curvature of the spine, which progressed steadily as he grew older. In 1892 he consulted the late Dr. Otto L. Schmidt, in Chicago, when the diagnosis of "heart trouble" was made. According to the patient's wife, he was at that time compelled to live a carefully regulated life but was subsequently able to play golf and to take long walks. For many years his life was not greatly disturbed. In 1917, at the age of 45, he consulted Dr. Walter Hamburger, who has placed at my disposal all his notes, which I am freely using in reconstructing the case history. From 1923 until his death the patient was under the care of Dr. Binswanger and myself. In no previously reported case has a patient with cardiac tumor lived so long or offered such a good opportunity for detailed study during life. The diagnosis was not made ante mortem. I repeatedly expressed the opinion that we were dealing with an unusual type of heart disease, but neither I nor any of the consultants suggested the correct diagnosis.

When the patient was first seen by Dr. Hamburger, he was recovering from a severe infection of the upper respiratory tract and complained of edema of the ankles. The urine contained much albumin and many casts; the heart was enlarged to the left. A soft diastolic murmur was heard along the left border of the sternum. The systolic blood pressure was 118. Later the character of the

25. Meroz, E.: A Clinical Study of Three Cases of Primary Tumor of the Heart, Internat. Clin. **4**:331, 1917.

26. Siegel, M. L., and Young, A. M.: Electrocardiographic Findings in Tumors of the Heart, with a Report of a Case, Am. Heart J. **8**:682, 1933.

murmur changed, so that the notes at various times read: "A soft postdiastolic murmur to the left of the sternum." "A soft presystolic-diastolic murmur."

In May 1920 the patient complained of shortness of breath. Extrasystoles were noted for the first time. The albumin and casts that were found in the urine in 1917 soon disappeared, but in 1920 they recurred. In June 1921 dyspnea was again present. The left border of the heart was found to be 2 fingerbreadths beyond the left nipple. The soft postdiastolic murmur was louder. The liver was enlarged but was not tender. Pitting edema of the ankles was noted. In January 1922 the liver was a full handbreadth below the costal margin. The heart measured 4 cm. to the right and 12.5 cm. to the left of the midsternum. The murmur was "soft, faint, presystolic, late in diastole and continuing to the first tone at the apex." The liver was still enlarged and not tender. The spleen was not felt. The renal function was not impaired.

It is to be emphasized at this point that the liver constantly remained enlarged a full handbreadth below the costal margin and was firm, round and never tender.

When the patient came under the care of Dr. Binswanger and myself, in 1923, he showed definite decompensation, and he complained of shortness of breath and edema of the ankles. These two symptoms were his main complaints at this time and later. Cyanosis, cough and rales in the chest were never prominent. He was not incapacitated for work. The examination showed, in brief, marked kyphoscoliosis and marked cardiac enlargement in all directions. The murmur was loud, was heard over the whole precordium and was definitely systolic. The systolic blood pressure varied between 130 and 140 and remained fairly constant all through his life. There was fibrillation at that time, and this also remained constant until his death.

Then began a series of remarkable changes in his condition. He made a spectacular recovery from this attack and was well and active until September 1925. Then another episode of dyspnea and edema occurred. Through 1926 and 1927 he worked full time, with only an occasional examination for routine check-up and with no noteworthy changes. In January 1928 he had pneumonia, involving the bases of both lungs; he was almost moribund but managed to survive. He remained in excellent condition until November 1929. Then symptoms of congestive failure recurred, followed by the usual recovery, which lasted until May 1932. From this time on more or less constant dyspnea, pedal edema and oppression in the chest with anginal pains were present. Although he was not confined to bed, there was definite and increasing restriction of his activity.

A new condition arose in 1927, when he began to complain of occasional precordial pains. At times these were typical anginal pains on effort; at other times they would occur when he was quietly sitting in bed.

In 1933 he began to complain of pain in the lower left quadrant of the abdomen, associated with frequent small stools containing pus and blood. Parasites were never found. These symptoms increased in severity.

On Dec. 6, 1935, severe acute abdominal pains developed, with bloody diarrheal stools. A barium sulfate enema revealed marked tubular encroachment of the sigmoid flexure, which resembled an inflammatory rather than a neoplastic lesion. Surgical intervention was considered, but the patient's general condition was too poor. Death occurred the next day, following symptoms of a ruptured intestine with peritonitis.

I have purposely avoided discussion of either the electrocardiograms or the roentgenograms because it seems more graphic to describe them separately. The roentgen examinations date from August 1921, when marked cardiac enlargement and some bulging of the arch of the aorta were noted.

In February 1922 there was a marked increase in the transverse diameter, and the aorta was broad. The right border of the heart was far beyond the usual normal limits, but there was marked scoliosis, which would account in part for the position of the heart. The left border of the heart was rather straight. The left ventricle appeared swollen.

In August 1922 the heart was 16.5 cm. in diameter and the chest 30 cm.

In October 1925 the heart was 18.8 cm. in diameter. It appeared swollen as in cases of pericarditis with effusion or myocarditis. The aorta was broad and dilated.

In December 1927 the heart was 20.4 cm. in diameter.

In October 1929 the heart was 21 cm. in diameter.

In May 1932 the heart was 22 cm. in diameter. What appeared to be the right border had a rippled contour, suggesting pericardial disease.

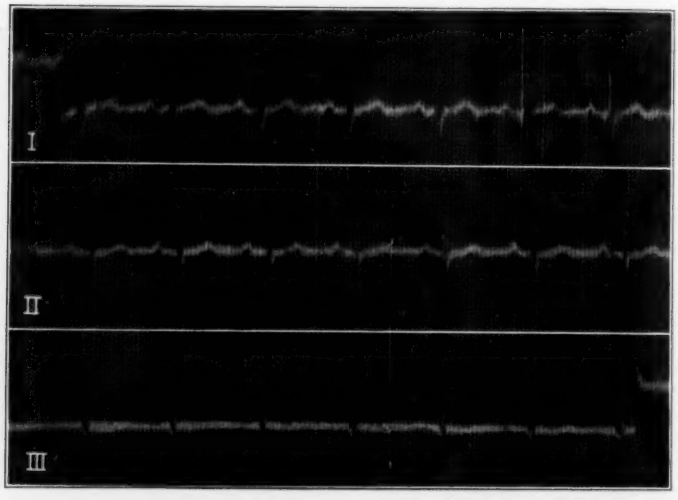

Fig. 1.—Sept. 18, 1919. A normal electrocardiogram.

On Dec. 6, 1935, fluoroscopic examination showed tremendous cardiac enlargement.

It is greatly to be regretted that, owing to legal restrictions on the preservation of x-ray films, none of the roentgenograms of this patient are available for reproduction. Measurements are lacking to substantiate our impression that the increase in the width of the right border of the heart noted in 1922 was constantly present. In fact, it seems in retrospect that not enough attention was paid by us to the changes in the right border.

We are able to present an unusual series of electrocardiograms, which graphically show the progressive cardiac changes (figs. 1 to 6).

Postmortem Examination.—A complete autopsy was performed one hour post mortem by Dr. Otto Saphir (Michael Reese Hospital, Chicago). The pathologic diagnosis was as follows: primary adenocarcinoma of the rectum with stricture formation; marked chronic and acute polypoid and ulcerating colitis and perfora-

tion of the upper portion of the sigmoid flexure; acute serofibrinopurulent peritonitis; primary myxoma of the right auricle; marked dilatation and hypertrophy of the right auricle; generalized arteriosclerosis; severe coronary sclerosis; slight narrowing of the ostium of the right coronary artery; arteriosclerosis of the aortic valve; fibrosis of the myocardium; chronic passive hyperemia of the liver [weight, 1,600 Gm.]; cloudy swelling of the liver and kidneys; arteriosclerotic scars of the kidneys; enlargement of the prostate; fibrosis of the spleen; edema of the ankles, and marked scoliosis of the vertebral column.

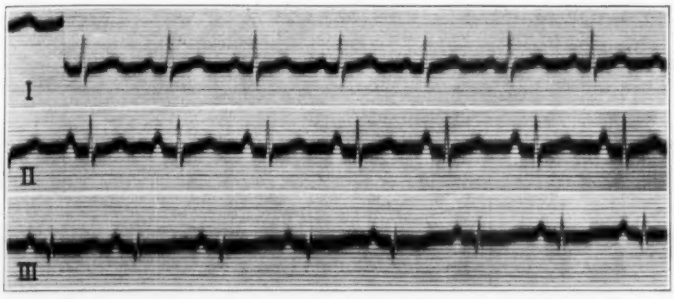

Fig. 2.—Jan. 11, 1921. P_2 and P_3 are extremely high and notched.

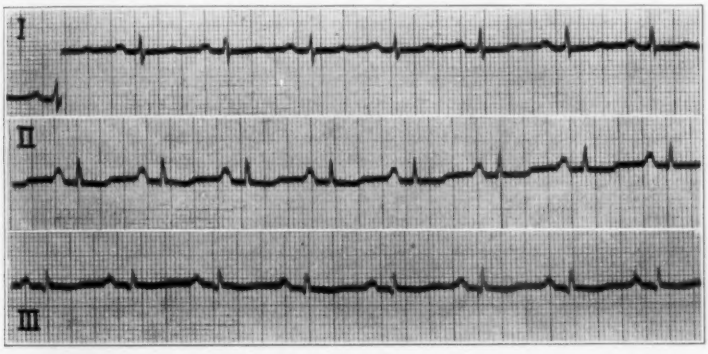

Fig. 3.—Aug. 14, 1922. P is enlarged and notched in all leads. T_2 is diphasic.

All details except those referring to the cardiac condition are omitted.

The heart was markedly enlarged and weighed 750 Gm. The epicardium was slightly granular over the region of the right auricle. However, the greater bulk of the heart seemed to be in the right auricle; the left ventricle was apparently no larger than usual. The right auricle contained a large spherical mass, about the size of an orange (measuring about 8 by 9 by 10 cm.). It was attached to the endocardium of the interauricular septum and almost completely filled the auricle. This tumor was semifirm, with a slightly gelatinous consistency. Through the upper layers of the mass, small, irregular, firm calcific masses could be felt. The

color of the tumor varied from a semitranslucent yellow-green to blood red. Sections taken from the tumor showed it to be of jelly-like consistency. The cavity of the right auricle was markedly dilated and its wall thickened. The endocardium of the rest of the heart showed no change. The cardiac valves showed no change with the exception of the aortic valve, which was markedly thickened

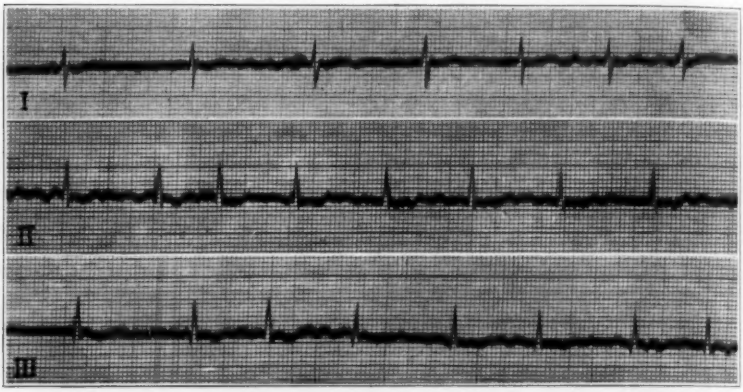

Fig. 4.—Oct. 12, 1925. The electrocardiogram shows auricular fibrillation, inversion (?) of T_3 and T_3 and preponderance of the right ventricle.

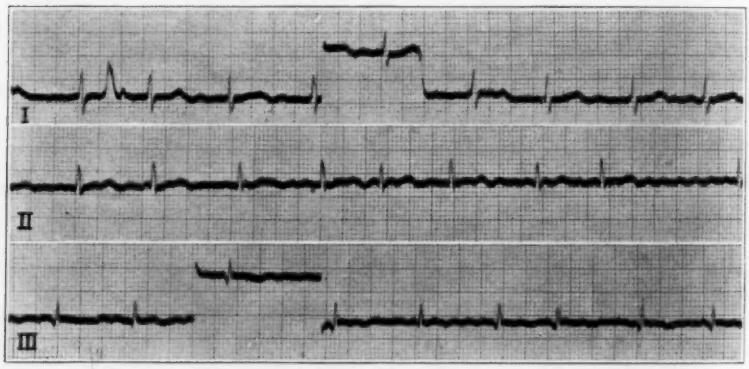

Fig. 5.—Dec. 30, 1927. There were auricular fibrillation, an auricular rate of 450, a ventricular rate of 90, an occasional left ventricular ectopic beat and a low amplitude of the ventricular complex.

by many yellow plaques. Many of these had a stonelike consistency, and the free borders of the cusps were also thick and sclerotic. The aortic leaflet of the mitral valve presented the same type of changes, but these did not extend down to the line of closure. The cardiac valves had the following circumferences:

aortic valve, 8.3 cm.; mitral valve, 10.5 cm.; pulmonary valve, 9.5 cm., and tricuspid valve, 15 cm. The left ventricle was not enlarged, and its wall measured up to 10 mm. in thickness. The right ventricle was not enlarged, but the tricuspid valve seemed to be dilated, and its wall measured up to 5 mm. in thickness. The line of demarcation between fat and muscles was not sharp. The right auricle was

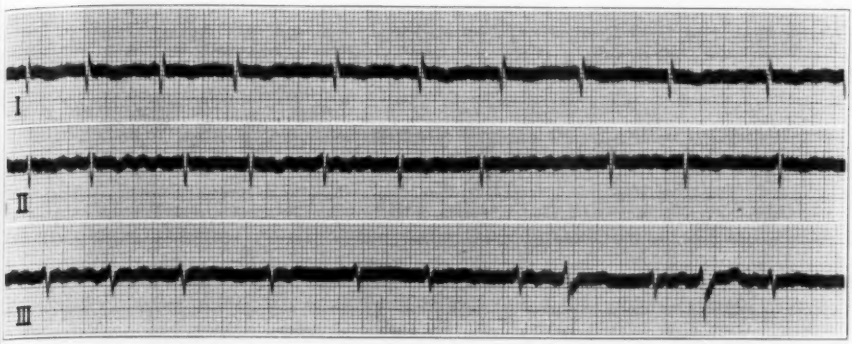

Fig. 6.—May 23, 1932. The findings were practically the same as those noted on Dec. 30, 1927 (fig. 5).

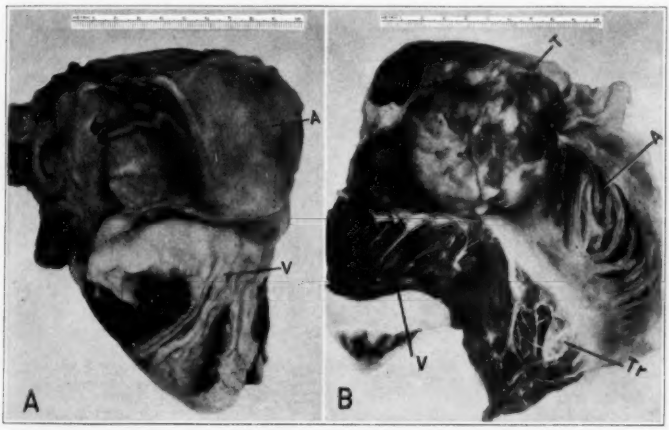

Fig. 7.—*A*, the right auricle and ventricle. Note the tremendous size of the auricle. *B*, the heart opened. *T* indicates tumor; *A*, auricle; *Tr.*, tricuspid valve, and *V*, right ventricle. Note the tumor of the auricle and the size of the ventricle as compared with the size of the auricle.

markedly dilated, its wall measuring 4.6 mm. in thickness. The pectinate muscles were hypertrophic. The aorta was covered by many yellow intimal plaques, and the mouth of the right coronary ostium was encroached on by some of these. The

coronary arteries were thick and cordlike, and the intima was covered by many yellow plaques that were often calcified. The first part of the anterior descending branch of the left coronary artery was markedly narrowed by these changes, but there was no complete occlusion.

Microscopic examination of the heart showed that most of the fibers stained irregularly in intensity. The paler fibers usually were lacking in nuclei and appeared hyalinized. Many of the fibers were fragmented along the lines of the intercalated disks. The larger vessels were markedly tortuous, and the lumens were narrowed by intimal proliferation. There was much newly formed connective tissue between the fibers of the cardiac muscle.

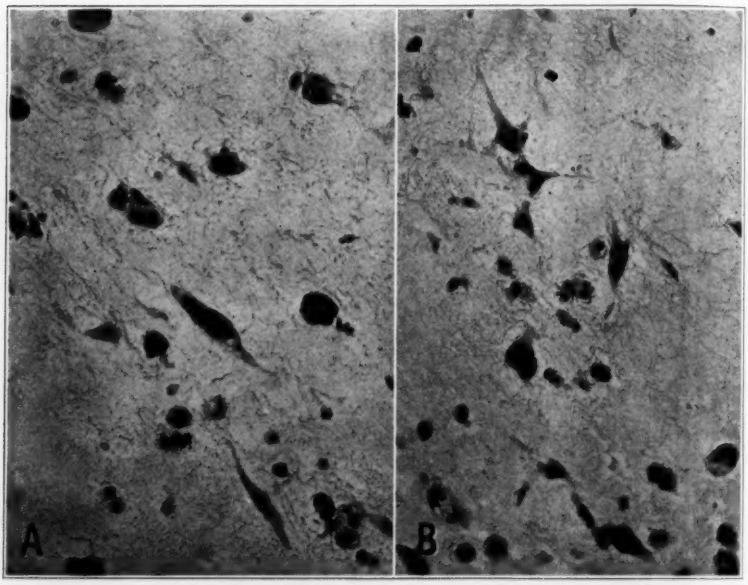

Fig. 8.—*A*, note the large amount of intercellular stroma and the oval cells with protoplasmic elongations. Hematoxylin and eosin preparation, × 400. *B*, section of the tumor. Note the triangular cells and the large amount of intercellular stroma; × 300.

The tumor of the heart, for the most part, showed in cross section an acellular material staining with various degrees of intensity, partly eosinophilic and partly basophilic. In a number of fields there were also cellular elements which were either oval or triangular, with processes extending in three directions, corresponding to the angles of the triangle. Also the oval cells had cytoplasmic elongations extending in two directions. Some of these cells were multinuclear. In some fields the eosinophilic material was slightly granular and occasionally vacuoles were present in this material as well as in the triangular cells. A number of well formed small and larger vessels were seen throughout the tumor. The periphery of the tumor, however, revealed tiny islets of vascular channels, sometimes incom-

pletely formed and lined with endothelial cells. In the periphery of the tumor there was also blood pigment, some of which was present in endothelial leukocytes and some free in the tissue. Sections which were stained with mucicarmine gave a positive reaction for mucin.

COMMENT

This paper records the history, physical findings and autopsy observations for a man aged 63 who had had "heart symptoms" for forty-three years. Death occurred from rupture of the colon. At the age of 20 the first symptoms of heart disease were noted. From that time until his death his life was a seesaw between periods of well-being and periods of illness. Serial roentgenograms and electrocardiograms are analyzed. At the age of 55 there were symptoms of angina pectoris. During the year preceding his death he had symptoms and signs of ulcerative colitis and, just before death, obstruction of the lower portion of the bowel, with perforation. The autopsy revealed, in summary, myxoma of the right auricle, high grade coronary and aortic sclerosis, ulcerative colitis with rupture and carcinoma of the rectum.

This story represents the longest case history on record of a tumor of the heart—forty-three years. The arteriosclerosis observed at autopsy gave symptoms only during the last seven or eight years of life and certainly represented a later development than the cardiac tumor. There is no way of ascertaining whether the myxoma was congenital or acquired. The early history suggests a strong possibility of a cardiac lesion in youth. The progressive increase in the size of the heart was probably due to a gradual increase in the size of the tumor. The electrocardiograms point strongly to the increasing amount of work done by the right auricle, with final cardiac exhaustion. During the later years of life, the heart was progressively unable to carry on its work, even when the activities of the patient were considerably reduced. Although death finally occurred from causes extraneous to the heart, the patient's cardiac mechanism was definitely showing signs of increasing inefficiency.

The diagnosis of benign tumor of the heart was not made during life. There are several outstanding features of the case which in retrospect seem to have greater importance than was attached to them during the life of the patient. The absence of a history of rheumatic involvement, the long duration of the illness, the long periods of well-being which intervened between attacks of congestive failure and the change in the character of the murmur are suggestive. The roentgen findings of a marked increase in the size of the right side of the heart, the absence of any electrocardiographic signs of preponderance of the left ventricle, the early presence of a high, notched P wave, the onset of auricular fibrillation and the constantly enlarging liver should have

directed our attention more forcibly to the right auricle. There were never any signs of thyrotoxicosis, nor was the picture ever typically that of the usual valvular diseases of the heart.

Previous investigators have emphasized the changeability of the murmur heard in cases of cardiac tumor. It will be recalled that Dr. Hamburger's notes reported such a variation during the earlier periods of this patient's life.

It is true that benign tumors of the heart are exceedingly rare and that none has been diagnosed ante mortem. An increasing number of reports on tumor of the heart are appearing in the literature, and it seems possible that, as has happened frequently with other rare conditions, consciousness of the anomaly may lead to more frequent diagnosis. Up to 1930 in only 1 case of metastatic tumor had the diagnosis been made ante mortem. Nine more cases were added in the next seven years. In 2 cases of primary malignant tumor the diagnosis was made ante mortem (in 1934 and 1935, respectively). It is hoped that this story may add to the possibility of the early diagnosis of primary benign tumor.

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BLOOD IN THROMBOANGIITIS OBLITERANS

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Bernhard,[1] in a study of 15 cases of thromboangiitis obliterans, found that the values for the calcium content of the serum and for the cholesterol, the chlorides and the carbon dioxide–combining power of the plasma were within normal limits. Three types of dextrose tolerance curves were found, but only 3 of the 15 patients appeared to have a diminished tolerance for dextrose. Heitz [2] studied 27 cases of "obliterating arteritis." Only 2 of these appeared to be characteristic examples of thromboangiitis obliterans (cases 12 and 13). The values for the cholesterol in these cases were 217 and 348 mg. per hundred cubic centimeters of plasma, respectively. Ssokoloff [3] found normal values for cholesterol in cases of "spontaneous gangrene" of the extremities.

Silbert, Kornzweig and Friedlander,[4] in a study of 69 cases of typical thromboangiitis obliterans, found an average volume of the whole blood of 64.3 cc. for each kilogram of body weight; this was an average reduction of 21 per cent in the value for normal persons, which is 82.7 cc. for each kilogram of body weight. The value for the hemoglobin in these 69 cases appeared to be greater than normal. As a result of these findings the authors drew the tentative conclusion that the blood is usually concentrated in thromboangiitis obliterans. In about 10 per cent of the cases the volume of blood was normal. However, the patients were exercised in order to insure a proper distribution of the dye in

* From the Division of Medicine, the Mayo Clinic.

1. Bernhard, A.: Summary of the Chemical Blood Findings in Thromboangiitis Obliterans, M. Rec. **97**:430-431 (March 13) 1920.

2. Heitz, J.: De la cholestérinémie chez les sujets affectes d'artéries oblitérans, Ann. de méd. **14**:378-409 (Nov.) 1923.

3. Ssokoloff, N. A.: Ueber den Cholesteringehalt des Blutes bei Spontangangrän der Extremitäten vor und nach der eiseitigen Epinephrektomie, Deutsches Arch. f. klin. Med. **144**:202-206 (June) 1924.

4. Silbert, S.; Kornzweig, A. L., and Friedlander, M.: Thrombo-Angiitis Obliterans (Buerger): IV. Reduction of Blood Volume, Arch. Int. Med. **45**:948-957 (June) 1930.

the body for the determination of the blood volume, a procedure which is not ordinarily used. Moreover, in the determination of the hematocrit value, 0.1 cc. of 20 per cent solution of potassium oxalate was used, which may have decreased the hematocrit values, as it has been shown that when dry potassium oxalate is used the volume of the erythrocytes is about 3 per cent less than when a dilute solution of potassium oxalate is used and correction is made in the final reading. No valid criticism can be offered of those two variations in technic, since they were apparently used in the study of both normal persons and patients with thromboangiitis obliterans.

Horton and Brown [5] reported 1 case in which thromboangiitis obliterans was associated with polycythaemia vera. This was the first case of the two diseases observed at the Mayo Clinic up to that time. Norman and Allen,[6] in a study of 98 cases of polycythaemia vera, did not find any instance of thromboangiitis obliterans. In a study of 35 cases of "relative polycythemia" they reported 5 instances of thromboangiitis obliterans. The hematocrit values varied from 51 to 63 per cent, and the blood volume varied from 63 to 88 cc. for each kilogram of body weight. Friedlander and Silbert,[7] in a study of 40 cases of thromboangiitis obliterans, found increases in the total ash content, in the values for the total protein and calcium in the serum and in the value for the cholesterol in the plasma. No striking abnormalities were found in the values for the chlorides in the plasma and for the sugar in the blood, and the results of tests for tolerance for sugar were normal. These authors expressed the opinion that there is a tendency toward concentration of the blood in thromboangiitis obliterans. Silbert and Friedlander [8] showed subsequently that the administration of thyroid increased the blood volume from 25 per cent below normal to normal levels in cases of thromboangiitis obliterans. On cessation of administration of thyroid the value for the blood volume returned to the original level. Subsequently, Friedlander, Laskey and Silbert [9] observed 25 patients who had undergone bilateral oophorectomy. These patients

5. Horton, B. T., and Brown, G. E.: Unusual Cases of Thrombo-Angiitis Obliterans: Their Association with Polycythemia Vera and Traumatic Myelitis, M. Clin. North America **12**:1617-1627 (May) 1929.

6. Norman, I. L., and Allen, E. V.: The Vascular Complications of Polycythemia, Am. Heart J. **13**:257-274 (March) 1937.

7. Friedlander, M., and Silbert, S.: Thrombo-Angiitis Obliterans (Buerger): VI. Chemistry of the Blood, Arch. Int. Med. **48**:500-506 (Sept.) 1931.

8. Silbert, S., and Friedlander, M.: Studies in Thrombo-Angiitis Obliterans (Buerger): VIII. Effect of Thyroid Administration on Blood Volume in Thrombo-Angiitis Obliterans, J. A. M. A. **97**:17-18 (July 4) 1931.

9. Friedlander, M.; Laskey, N., and Silbert, S.: Reduction of Blood Volume Following Bilateral Oophorectomy, Proc. Soc. Exper. Biol. & Med. **30**:1263-1264 (June) 1933.

were found to have an average blood volume that was 25 per cent less than normal. Coincident with this there was an increase in the amount of cholesterol and fibrinogen in the blood plasma. They concluded that the ovaries produce some substance capable of influencing the blood volume. Rabinowitz and Kahn [10] found that the normal value for the phospholipids was 203 mg. for each hundred cubic centimeters of plasma and that the value in cases of thromboangiitis obliterans was 236 mg. per hundred cubic centimeters of plasma.

MATERIAL STUDIED

A study was made of the various components of the blood of 105 patients with thromboangiitis obliterans observed at the clinic; 76 of the patients were gentiles and 29 were Jews. The studies were made only for patients who showed characteristic symptoms and clinical manifestations of thromboangiitis obliterans. Patients who apparently had mixed arterial lesions, both degenerative and inflammatory, and those whose arterial lesions were solely arteriosclerotic were excluded from this study.

METHODS OF STUDY

The blood volume was determined by means of the Rowntree, Brown and Roth [11] modification of the Keith, Rowntree and Geraghty [12] method. All the determinations in this study as well as those reported in the monograph by Rowntree, Brown and Roth were made by one person (Dr. Roth), who has made approximately one thousand determinations. The value for the calcium in the serum was determined by the Clark-Collip [13] modification of the Kramer-Tisdall [14] method; the value for the blood urea, by the method of Van Slyke and Cullen; [15] the value for the inorganic phosphorus in the serum, by the method of Fiske and Subbarow; [16] the values for cholesterol and total fats in the plasma, by the methods of Bloor,[17]

10. Rabinowitz, H. M., and Kahn, J.: Relationship of Phospholipin Metabolism to Thromboangiitis Obliterans and Its Treatment, Am. J. Surg. **31**:329-339 (Feb.) 1936.

11. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma, Philadelphia, W. B. Saunders Company, 1929.

12. Keith, N. M.; Rowntree, L. G., and Geraghty, F. J.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547-576 (Oct.) 1915.

13. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for Determination of Blood Serum Calcium, with a Suggested Modification, J. Biol. Chem. **63**:461-464 (Jan.) 1925.

14. Kramer, B., and Tisdall, F. F.: A Simple Technique for the Determination of Calcium and Magnesium in Small Amounts of Serum, J. Biol. Chem. **47**:475-481 (June) 1921.

15. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease, and Its Use in the Determination of Urea, J. Biol. Chem. **19**:211-228 (July) 1914.

16. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375-400 (Dec.) 1925.

17. Bloor, W. R.: The Determination of Cholesterol in Blood, J. Biol. Chem. **24**:227-231 (March) 1916; The Determination of Small Amounts of Lipid in Blood Plasma, ibid. **77**:53-73 (April) 1928.

and the value for lecithin in the plasma, by the method of Whitehorn.[18] The value for the serum protein was determined by the macromethod of Kjeldahl.

RESULTS

Blood Volume.—The total volume of whole blood was determined for 55 patients: 40 gentiles and 15 Jews. In 2 cases a limb had been amputated. For the entire group the volume of blood varied from 4,305 to 7,113 cc., and for each kilogram of body weight it varied from 59 to 109 cc. The respective averages were 5,541 and 80.2 cc. The blood volume of the Jews varied from 4,305 to 7,113 cc., and for each kilogram of body weight it varied from 59 to 97 cc. The respective averages were 5,234 and 74.1 cc. The blood volume of the gentiles varied from 4,420 to 6,645 cc., and for each kilogram of body weight it varied from 61 to 109 cc. The respective averages were 5,670 and 82.8 cc. (table 1).

TABLE 1.—*Average Hematocrit Value and Blood Volume in Thromboangiitis Obliterans*

No. of Cases	Race	Weight, Kg.	Height, Cm.	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.
55	Gentiles and Jews	66.8	7.02	46.5	5,541	80.2	3,058	2,941.0	42.8	1,642.0
40	Gentiles	67.8	69.2	46.7	5,670	82.8	3,155	2,995.9	44.0	1,665.0
15	Jews	65.0	72.6	46.1	5,234	74.1	2,960	2,810.0	39.9	1,586.8

In contrast with these figures are the values for the total blood volume when this same group of patients, irrespective of nationality, was divided into three groups according to body build. The first group included the patients who were overweight, the second group included those who were of standard weight and the third group included those who were underweight. Classification of these groups was made as follows: The patients who were considered of standard weight were those whose weight, taking into consideration sex, height and age, varied less than 10 per cent from the actuarial figures commonly in use. The patients who were underweight and overweight were those whose weights varied more than 10 per cent from the actuarial figures. The blood volume of the underweight patients varied from 4,305 to 6,394 cc., and for each kilogram of body weight it varied from 69 to 109 cc. The respective averages were 5,331 and 91 cc. (table 2). The blood volume of the patients of normal weight varied from 4,035 to 6,850 cc., and for each kilogram of body weight it varied from 59 to 101 cc. The

18. Whitehorn, J. C.: A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J. Biol. Chem. **62**:133-138 (Nov.) 1924.

respective averages were 5,496 and 78.6 cc. (table 3). The blood volume of the patients who were overweight varied from 4,361 to 7,113 cc., and for each kilogram of body weight it varied from 54 to 84 cc.

TABLE 2.—*Hematocrit Values and Blood Volume for Underweight Patients*

Case	Age, Yr.	Weight, Kg.	Height, Cm.	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.
1	44	61	68	47	6,062	99	3,590	3,233	53	1,890
2	45	56	66	48	5,118	91	3,160	2,660	48	1,610
3	42	63	66	41	5,895	94	3,388	3,478	55	1,999
4	30	65	71	45	5,545	85	3,047	3,050	47	1,676
5	44	57	70	44	5,282	93	3,107	2,958	52	1,740
6	43	60	67	46	4,873	81	2,901	2,632	44	1,567
7	34	46	66	58	5,660	109	3,605	2,375	46	1,513
8	45	66	70	44	4,560	69	2,519	2,236	35	1,235
9	37	61	67	50	4,654	78	2,738	2,327	38	1,369
10	49	60	69	43	5,470	91	3,199	3,115	48	1,822
11	29	57	68	36	5,800	102	3,473	3,715	65	2,225
12	38	63	68	53	6,394	102	3,675	3,005	48	1,727
13	46	57	64	46	6,002	105	3,808	3,290	57	2,056
14	38	57	68	45	4,670	82	2,800	2,565	45	1,535
15	25	54	66	47	4,920	91	3,075	2,605	48	1,627
16	29	50	63	43	4,305	86	2,851	2,454	49	1,625
Average	38.6	58.3	67.3	46	5,331	91.1	3,183	2,862	48.3	1,704

TABLE 3.—*Hematocrit Values and Blood Volume of Patients of Normal Weight*

Case	Age, Yr.	Weight, Kg.	Height, Cm.	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.
1	51	75	68	46	5,960	79	3,185	3,215	43	1,718
2	38	65	64	43	4,420	67	2,600	2,500	39	1,470
3	41	83	69	46	5,929	71	3,060	3,197	39	1,620
4	43	69	66	48	5,005	73	2,796	2,608	38	1,454
5	39	70	68	42	5,754	82	3,162	3,337	48	1,833
6	42	90	72	44	6,201	69	2,925	3,477	39	1,640
7	35	73	68	43	5,763	79	3,115	3,285	43	1,776
8	35	65	69	42	5,930	91	3,350	3,435	53	1,941
9	44	71	69	40	6,205	88	3,409	3,170	45	1,741
10	24	68	67	50	5,394	70	2,982	2,697	40	1,466
11	35	69	66	51	4,906	71	2,823	2,448	35	1,383
12	40	59	63	51	5,418	92	3,426	2,652	45	1,678
13	53	70	60	57	5,114	73	3,060	2,190	31	1,325
14	27	58	66	49	5,100	88	3,001	2,599	46	1,575
15	47	80	71	42	5,840	73	2,985	3,385	42	1,701
16	35	78	68	51	6,645	86	3,500	3,265	43	1,715
17	23	68	70	44	6,850	101	3,723	3,840	56	2,087
18	54	71	64	41	5,001	70	2,825	2,950	42	1,667
19	25	59	64	47	4,422	75	2,730	2,345	40	1,448
20	39	70	68	44	4,035	59	2,970	2,219	32	1,661
21	49	66	66	47	4,840	73	2,813	2,565	40	1,491
22	47	76	67	45	5,810	70	2,855	2,920	38	1,570
23	53	65	63	51	5,750	88	3,464	2,820	44	1,699
24	47	62	56	50	6,020	97	3,562	3,010	49	1,781
Average	40.3	70	66.1	46.8	5,496	78.6	3,007	2,922	42.1	1,643

The respective averages were 5,857 and 70.6 cc. The hematocrit values of the entire group studied varied from 40 to 58 per cent; the average was 46.5 per cent (table 1). There was no significant difference in the values for Jews and gentiles (46.1 and 46.7 per cent, respectively; table 1) or for the subjects who were of normal weight, overweight or underweight (46.8, 46.6 and 46 per cent, respectively; tables 2 to 4).

Serum Calcium.—The values for serum calcium were determined for 55 patients, 41 gentiles and 14 Jews. The average ages of the gentiles and of the Jews were 37.8 and 39.2 years, respectively. No significant variation from normal was found (table 5).

Inorganic Phosphorus.—The values for inorganic phosphorus were determined for 50 patients, 38 gentiles and 12 Jews. The average ages

TABLE 4.—*Hematocrit Value and Blood Volume of Overweight Patients*

Case	Age, Yr.	Weight, Kg.	Height, Cm.	Hematocrit Value, per Cent	Blood			Plasma		
					Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.	Volume, Cc.	Cc. per Kg.	Cc. per Sq.M.
1	48	77	64	51	5,470	71	3,020	2,680	35	1,480
2	34	77	76	47	6,075	79	2,975	3,220	42	1,576
3	34	82	69	45	5,305	65	2,693	2,920	36	1,480
4	43	77	67	44	6,441	84	3,447	3,607	47	1,915
5	51	79	67	50	5,950	76	3,132	2,975	38	1,566
6	42	84	62	51	6,919	82	3,740	2,542	41	1,374
7	42	91	69	47	5,562	61	2,710	2,948	32	1,436
8	44	78	67	40	5,810	75	3,058	3,485	44	1,834
9	49	96	69	48	6,280	66	2,845	3,265	34	1,502
10	35	77	66	47	5,996	78	3,220	3,178	41	1,707
11	44	81	68	48	4,361	54	2,260	2,268	28	1,175
12	35	79	64	43	5,270	67	2,849	2,995	38	1,619
13	52	78	66	48	5,450	70	2,914	2,830	36	1,513
14	44	120	67	44	7,113	60	3,161	3,983	34	1,770
Average	42.7	84	67.2	46.6	5,857	70.6	3,002	3,064	37.6	1,568

TABLE 5.—*Values for Calcium, Inorganic Phosphorus, Cholesterol, Lecithin, Fatty Acids and Total Lipoids in Thromboangiitis Obliterans*

Patients	Calcium, Mg. per 100 Cc. of Serum		Inorganic Phosphorus, Mg. per 100 Cc. of Serum		Lipoids, Mg. per 100 Cc. of Plasma							
					Cholesterol		Lecithin		Fatty Acids		Total Lipoids	
	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range	Average	Range
Total.....	10.3	8.8-11.7	3.5	2.5-4.5	192.4	102-273	244.0	182-365	377.5	194-603	563.8	360-871
Gentiles.....	10.1	8.8-11.6	3.4	2.5-4.4	184.4	102-273	236.0	182-312	371.6	194-603	549.8	360-871
Jews.....	10.8	9.7-11.7	3.6	2.8-4.5	215.6	133-273	274.6	208-365	395.3	280-497	605.6	413-770

of the two groups of patients were 37.8 and 39.2 years, respectively. No significant variations from normal were found (table 5).

Lipoids.—The values for the plasma cholesterol were determined for 43 patients, 32 gentiles and 11 Jews (table 5). The concentration of lecithin in the blood plasma was determined for 24 patients, 19 gentiles and 5 Jews (table 5). The values for the fatty acids and total lipoids in the blood plasma were determined for 36 patients, 27 gentiles and 9 Jews (table 5). The average ages of the patients in the two groups were 37.4 and 40.8 years, respectively.

Blood Urea.—The concentration of urea in the blood was determined in 40 cases. The average value was 26.9 mg. per hundred cubic

centimeters of blood, and the values ranged from 14 to 46 mg. per hundred cubic centimeters. These values are considered normal.

Serum Protein.—The values for the serum protein were determined in 12 cases. The average value was 6.4 Gm. per hundred cubic centimeters, and the values ranged from 5 to 8.7 Gm. per hundred cubic centimeters. These are considered normal values.

COMMENT

Our studies indicate that the values for the blood urea, serum calcium, protein and inorganic phosphorus are normal in cases of thromboangiitis obliterans. The average hematocrit value (46.5 per cent) in 54 cases was near the upper limits of normal, but the hematocrit value exceeded 50 per cent in only 9 instances. In a study of 49 normal men of various body build, Rowntree, Brown and Roth found that the hematocrit value varied from 36 to 47 per cent; the average was 42 per cent. However, Haden [19] said that a normal erythrocyte count of 5,000,000 per cubic millimeter of blood gives a hematocrit value of 48 per cent. The difficulty in evaluating the significance of our figures is chiefly one of accepting a normal value for purposes of comparison. Certainly, many of the values determined can be accepted as normal, and the significance of those which seem somewhat greater than normal can be challenged chiefly because they lie so close to the normal range. One conclusion seems entirely warranted; namely, there are no characteristic changes in the hematocrit value in cases of thromboangiitis obliterans.

The average value which we have found for the blood volume for each kilogram of body weight (91.1 cc.) for patients who were underweight agrees with the average figure (92 cc.) determined for underweight patients by Rowntree, Brown and Roth. However, a variation in the value for patients of normal weight (78.6 cc. for each kilogram of body weight) is less than that (89.1 cc. for each kilogram of body weight) found for patients of similar body build by Rowntree, Brown and Roth. Moreover, the values obtained in our studies of this group were less than the average values found by Rowntree, Brown and Roth for 20 of the 24 patients. This finding seems perhaps more significant when one considers that the average weight of our group of patients (70 Kg.) was about the same as that of the normal persons (69.1 Kg.) studied by Rowntree, Brown and Roth. The average values for the blood volume of the overweight patients in our cases was 70.6 cc. per kilogram of body weight; the value for patients of similar body build who were studied by Rowntree, Brown and Roth was 81.8 cc. In 12 of our 14 patients in this group the value was less than the average

19. Haden, R. L.: Accurate Criteria for Differentiating Anemias, Arch. Int. Med. **31**:766-780 (May) 1923.

determined by Rowntree, Brown and Roth. However, the average weight for our group (84 Kg.) was substantially greater than that of the patients studied by Rowntree, Brown and Roth, which was 77.6 Kg.

It is apparent that no far reaching conclusions may be drawn from these studies, for the blood volume of underweight patients who have thromboangiitis obliterans appears normal while that of patients of normal weight and those who are overweight appears to be decreased. Certainly, the conclusion advanced by Friedlander and Silbert, that the blood seems to be concentrated in thromboangiitis obliterans, seems on a none too secure basis. Since thromboangiitis obliterans causes occlusion of arteries and veins, the explanation for a decrease in the blood volume in many cases may lie in the diminished volume of the vascular tree rather than in concentration of the blood. Silbert, Kornzweig and Friedlander considered this possibility and apparently eliminated it by finding normal blood volumes in cases in which occlusive arterial disease was the result of arteriosclerosis. However, it must be kept in mind that veins are not occluded in arteriosclerotic disease but that they may be occluded in thromboangiitis obliterans. It is well known from anatomic and arteriographic studies (Allen and Barker [20]) that the veins of the extremities occupy much more space than do the arteries and that a disease which occludes both arteries and veins might cause a discernible reduction in blood volume, while one which involves arteries alone might not do so. It is true, certainly, that many patients who have characteristic thromboangiitis obliterans have a normal blood volume; this observation alone casts some doubt on the assumption that diminished blood volume is an integral part of thromboangiitis obliterans.

Studies of the concentration of cholesterol in the plasma of normal persons have demonstrated a great variation and a wide range. Denis,[21] Bloor,[22] Bruger and Poindexter,[23] McGee,[24] Boyd [25] and Page and his

20. Allen, E. V., and Barker, N. M.: Roentgenologic Visualization of the Veins of the Extremities: Preliminary Description of a Method, Proc. Staff Meet., Mayo Clin. **9**:71-74 (Jan. 31) 1934.

21. Denis, W.: Cholesterol in Human Blood Under Pathological Conditions, J. Biol. Chem. **29**:93-110 (Feb.) 1917.

22. Bloor, W. R.: The Distribution of the Lipoids ("Fat") in Human Blood, J. Biol. Chem. **25**:577-599 (July) 1916.

23. Bruger, M., and Poindexter, C. A.: Relation of Plasma Cholesterol to Obesity and to Some of the Complicating Degenerative Diseases (Diabetes Mellitus, Essential Hypertension, Osteo-Arthritis and Arteriosclerosis), Arch. Int. Med. **53**:423-434 (March) 1934.

24. McGee, L.: Blood Cholesterol in Disturbances of Basal Metabolic Rate, Ann. Int. Med. **9**:728-738 (Dec.) 1935.

25. Boyd, E. M.: A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, J. Biol. Chem. **101**:323-336 (June) 1933.

co-workers [26] found that the range of normal values was 150 to 260 mg. per hundred cubic centimeters. Page, Kirk, Lewis, Thompson and Van Slyke,[27] who used a gasometric method of determination, found a mean value of 232 mg. per hundred cubic centimeters. Bruger and Poindexter indicated that the range between 230 and 250 mg. is suggestive of hypercholesteremia. In a study of 32 normal persons we found that the average value was 180.8 mg. per hundred cubic centimeters and that the range was from 135 to 262 mg. per hundred cubic centimeters. In only 2 of the 43 cases of thromboangiitis obliterans which we studied did the values for cholesterol exceed the highest values found in our study of normal persons. De Langen [28] reported a series of observations made for natives of Java, China, Japan and India. The cholesterol content of the blood of these natives was found to average 40 to 50 per cent less than that of the blood of Europeans. This corresponded closely with the diet of the natives, which is poor in cholesterol, a customary feature in their respective countries. Bloor [29] also said that the greatest single factor influencing the concentration of the lipids in the plasma appears to be diet, particularly the amount of fat which the food contains.

The question arose as to whether there is any great difference in the diet of gentiles and Jews, and if so, whether it is sufficient to produce a significant increase in the cholesterol content of the plasma. Whereas in our study of patients with thromboangiitis obliterans the average value for the cholesterol in the plasma of Jews was 31.2 mg. per hundred cubic centimeters higher than that of the gentiles, the values were still within normal limits. Hypercholesteremia has been reported to be associated with obesity; however, in most instances the obesity was complicated by some degenerative disease. In other instances normal values have been reported for cholesterol. Bruger and Poindexter in 11 per cent of 53 cases of uncomplicated obesity found that the value for cholesterol was more than 250 mg. per hundred cubic centimeters of plasma. McGee observed normal values in 20 cases of obesity. In our group of cases in which thromboangiitis obliterans was associated with obesity, the average value for cholesterol was 180 mg. per hundred cubic centimeters of plasma; the values ranged from 102 to 273 mg.

26. Page, I. H.; Pasternack, L., and Burt, M. L.: Ueber den Transport von Fetten und Lipoiden durch Blut nach Oeleingabe, Biochem. Ztschr. **223**:445-456, 1930.

27. Page, I. H.; Kirk, E.; Lewis, W. H., Jr.; Thompson, W. R., and Van Slyke, D. D.: Plasma Lipids of Normal Men at Different Ages, J. Biol. Chem. **111**:613-639 (Nov.) 1935.

28. de Langen, C. D.: Échanges cholestériniques et pathologie de la race, Presse méd. **24**:332-333 (July 27) 1916.

29. Bloor, W. R.: Diet and the Blood Lipids, Proc. Soc. Exper. Biol. & Med. **28**:701-702 (Feb.) 1931.

per hundred cubic centimeters. Obesity apparently did not influence the cholesterol values.

In our cases of thromboangiitis obliterans the average value for lecithin per hundred cubic centimeters of plasma was 38.6 mg. higher for the Jewish patients than it was for the gentiles, but the average values for both groups of patients were within normal limits.

Page and his co-workers reported that the average value for fatty acids in the plasma of normal persons was 360.1 mg. per hundred cubic centimeters and that the values ranged from 234.1 to 490.7 mg. per hundred cubic centimeters. Man and Gildea [30] reported an average value of 363.8 mg. per hundred cubic centimeters but a slightly higher range of 287.6 to 451 mg. per hundred cubic centimeters. In our study of patients with thromboangiitis obliterans we found that the average value for fatty acids for Jewish patients was 23.7 mg. per hundred cubic centimeters of plasma higher than it was for gentile patients. In our study of 36 patients with thromboangiitis obliterans, a value for fatty acids in excess of that given as the upper normal limit by Man and Gildea was found in only 9 cases. The average value of 377 mg. per hundred cubic centimeters obtained in our study is slightly in excess of the average of 360 mg. found by Page and his co-workers and the average of 363 mg. found by Man and Gildea in a study of normal persons.

Valuation of our studies of the cholesterol and fatty acids in the plasma in cases of thromboangiitis obliterans is handicapped by the uncertainty as to what constitutes normal values and also by the wide range of normal values. Certainly, our figures vary little from the values considered normal, and while in some instances our values definitely exceed those given for normal persons, in most instances they lie well within the accepted normal range. Since this is true, we can say unequivocally that there is no characteristic change in the concentration of cholesterol or fatty acids in the plasma of patients with thromboangiitis obliterans.

SUMMARY

The values for serum calcium, serum protein, blood urea, serum lecithin and serum phosphorus were found to be within normal limits in our study of the blood in cases of thromboangiitis obliterans. In most instances the blood volume, hematocrit value and concentration of fatty acids and cholesterol in the plasma were found to be normal. In some instances the blood volume was slightly decreased, and the hematocrit value and the concentration of fatty acids and cholesterol in the plasma were slightly increased. We doubt the significance of these findings, since they are inconstant findings in thromboangiitis obliterans.

30. Man, E. B., and Gildea, E. F.: The Effect of the Ingestion of a Large Amount of Fat and of a Balanced Meal on the Blood Lipids of Normal Man, J. Biol. Chem. **99**:61-69 (Dec.) 1932.

BILATERAL CORTICAL NECROSIS OF THE KIDNEYS

REPORT OF THREE CASES

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The first description of bilateral cortical necrosis of the kidneys is accredited to Juhel-Rénoy,[1] of France (1886). The condition is rare, the literature containing reports of about 70 cases. Reviews of the literature have been made by Scriver and Oertel[2] (1930), Ash[3] (1933) and Evans and Gilbert[4] (1936).

Bilateral cortical necrosis of the kidneys is so named because at autopsy both kidneys show more or less extensive necrosis of the cortex. Grossly the necrotic cortex is reddish yellow and soft, closely resembling a fresh infarct in appearance and consistency. However, the involved area does not have the shape of an infarct but has the shape of the cortex even to the point of involving the columns of Bertin. Only a thin layer of cortex adjacent to the capsule and the pyramids is spared. The necrosis is more or less patchy. The cortical vessels also are necrotic and contain thrombi, the composition, distribution, origin and significance of which are the cause of much debate. The liver usually shows cloudy swelling; in some cases, more especially those in which the condition is associated with dioxane poisoning, there is central necrosis of the liver.

The etiology of bilateral cortical necrosis of the kidneys has been the subject of much investigation. As far as can be determined, the condition affects previously normal kidneys. In the majority of cases there has been the complication of pregnancy, often associated with

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1. Juhel-Rénoy, E.: De l'anurie précoce scarlatineuse, Arch. gén. de méd. **17**:385-410, 1886.

2. Scriver, W. de M., and Oertel, H.: Necrotic Sequestration of the Kidneys in Pregnancy (Symmetrical Cortical Necrosis): Clinical and Anatomic-Pathogenetic Study, J. Path. & Bact. **33**:1071-1094 (Oct.) 1930.

3. Ash, J. E.: Bilateral Cortical Necrosis of the Kidneys (Angioneurotic Anuria), Am. J. M. Sc. **185**:71-86 (Jan.) 1933.

4. Evans, N., and Gilbert, E. W.: Symmetrical Cortical Necrosis of the Kidneys: Report of a Case, Am. J. Path. **12**:553-560 (July) 1936.

antepartum hemorrhage. In other instances the condition has been associated with infectious diseases, trauma, the intravenous use of camphor and dioxane poisoning. In several cases no other disease has been demonstrable. Persons from 13 to 65 years of age have been affected, the average age being 32 (Evans and Gilbert).[4]

The pathogenesis of the condition is obscure. It is generally agreed that there is a disturbance of the vascular supply of the cortex, but whether this is due to multiple emboli, pressure, thrombosis, arteritis, necrosis of vessels or vascular stasis is not settled.

The clinical picture in cases of bilateral cortical necrosis of the kidneys is fairly characteristic. As has been stated, the disease usually occurs in pregnant women, most commonly during the latter part of pregnancy. In a lesser number of cases the disease affects males or nonpregnant females. The onset is usually sudden. The paramount symptom is anuria. Of lesser diagnostic import are headache, nausea, vomiting and epigastric pain and occasionally edema and convulsions. The urine, if any is passed, contains albumin and casts, and occasionally blood and pus. The blood pressure usually remains normal but may go up or down. There is retention in the blood of nitrogenous products.

In the differential diagnosis, nephritis, renal infarction and bilateral ureteral occlusion are to be considered. In nephritis the onset is more gradual, anuria is less common and the course is usually less dramatic. Renal infarction is more likely to be accompanied by pain, the anuria is not so constant and there usually is evidence of associated cardiovascular disease. Bilateral ureteral obstruction can be differentiated by careful urologic examination.

Bilateral cortical necrosis is usually fatal. However, a few cases of supposed bilateral involvement with recovery are reported. The treatment usually consists of the intravenous administration of dextrose and the forcing of fluids.

Three cases of bilateral cortical necrosis of the kidneys have been encountered at the Cleveland City Hospital in the past four years. These cases are of particular interest because the condition was not associated with pregnancy and because in all 3 cases it was associated with severe central necrosis of the liver.

REPORT OF CASES

CASE 1.—G. P., a 40 year old Hungarian laborer, entered the Cleveland City Hospital on July 20, 1933, with a complaint of pain in the stomach of two days' duration. He stated that on July 18 (two days before entry) he drank an undetermined amount of "almond extract." A few hours later diffuse abdominal pain and complete anuria developed.

Physical examination showed the patient to be seriously ill, the respiration was rapid and deep, and the temperature was normal. The optic disks were edematous. There were rales at the bases of both lungs. An apical systolic murmur was

audible. The blood pressure was 132 systolic and 68 diastolic. The abdomen was diffusely tender, and the edge of the liver was palpable 5 cm. below the costal margin.

By catheterization no urine was obtained. The value for urea nitrogen was 140 mg. per hundred cubic centimeters of blood; the value for creatinine was 14.5 mg. The icteric index was 27. The carbon dioxide-combining power was 9 volumes per cent. The Wassermann reaction of the blood was 4 plus; the Kline test of the blood gave a negative reaction. The leukocytes numbered 14,500 per cubic millimeter. The red blood cell count and the hemoglobin value were normal.

The patient remained anuric, became progressively lethargic and died eighteen hours after admission to the hospital.

The clinical diagnosis was acute toxic hepatitis and acute toxic nephritis due to poisoning, with terminal bronchopneumonia.

The autopsy was performed two hours after death. The body was that of a well nourished man whose external features were not remarkable. There was no peripheral edema.

None of the body cavities contained an excess of fluid.

The lungs revealed bronchopneumonia, greatest in extent in the lower lobe of the right lung.

The liver weighed 2,600 Gm. Its edges were rounded and extended 4 cm. below the costal margin in the midclavicular line on the right. The capsule was thin, smooth and glistening. The cut surface bulged, it was bloody and of uniform tan color and the architecture was obscured. Microscopic examination showed severe central necrosis; in the necrotic areas the cells had lost their normal architecture, the nuclei were pyknotic or absent, the cytoplasm was granular and the cells had the appearance of "ghosts" of hepatic parenchyma. The periphery of each lobule showed early parenchymatous degeneration. The prominent feature was the absence of any cellular reaction or of proliferation of bile ducts.

The kidneys were similar. They were enlarged, and the capsule stripped with ease, leaving a smooth surface that was mottled, the color varying from reddish gray to purplish red. The cortex and the pyramids were well demarcated. The former measured 6 mm. and the latter 23 mm. in thickness. The cortical striations were seen only in scattered areas. The intervening areas consisted of purplish red amorphous tissue, portions of which were yellowish white. There was a narrow hyperemic and hemorrhagic zone between the cortex and the pyramids. These same changes were more extensive in the columns of Bertin. The renal pelvis was not unusual.

Microscopic examination revealed a patchy distribution of cortical necrosis, each area resembling a bland infarct. Both the tubular and the glomerular structures showed complete degeneration and loss of structure. Between these areas of necrosis the cortex was not abnormal. About each area was evidence of moderate polymorphonuclear reaction. There was a zone of hemorrhage between the cortex and the pyramids. About half the arteries in the necrotic area showed necrosis of their walls and thrombosis.

The other organs were not abnormal.

Case 2.—J. M., a 53 year old housewife, was admitted to the Cleveland City Hospital on April 24, 1936. She was unconscious. Her relatives stated that she had been in good health until six days before entry when anuria and intractable nausea and vomiting developed. These symptoms were associated with continuous epigastric pain which radiated through to the back. The patient became

increasingly drowsy and finally comatose. She was said to have had hypertension for several years. She was a chronic alcoholic addict but had had no liquor for four days prior to the onset of her illness.

Examination showed the patient to be dying. The fundi showed slight vascular disease. The blood pressure was 160 systolic and 85 diastolic. The heart and lungs were normal. The edge of the liver was palpable 6 cm. below the costal margin. The skin was not icteric.

Catheterization yielded 4 cc. of urine. This was light amber and showed an alkaline reaction; it contained albumin of grade 3. Microscopically the uncentrifuged specimen showed 20 to 30 white blood cells and an occasional red blood cell per high power field. The benzidine test for blood in the urine gave a negative reaction. The stool was normal in appearance; it contained bile and gave a negative reaction with the benzidine test. Blood culture showed no growth. The value for urea nitrogen was 227.6 mg. per hundred cubic centimeters of blood; the value for creatinine was 12.6 mg. The Kline and the Wassermann test of the blood both showed a 4 plus reaction.

The patient died forty-five minutes after admission to the hospital. The clinical diagnosis was uremia of undetermined origin.

The autopsy was performed eighteen hours after death. The body was that of a well developed woman whose external features were not remarkable. There was no peripheral edema.

The heart weighed 275 Gm. There was typical syphilitic aortic valvulitis with widening of the commissures. The aorta showed marked syphilitic aortis throughout the thoracic portion. The intima was scarred, and there were several small aneurysms which bulged outward 2 to 3 mm. Microscopic examination revealed the characteristic perivascular plasma cell infiltration and increased vascularity of the media.

The liver weighed 1,600 Gm. The capsule was thin, smooth and glistening. Beneath the capsule were numerous small petechiae, which were most numerous over the anterior surface of the right lobe. The cut surface of the liver was a light tan and showed an occasional small hemorrhage. The architecture was obscured. Microscopic examination revealed severe central necrosis, as was seen in case 1. Again the absence of evidence of cellular reaction was noted.

The gallbladder contained two small calculi, but there was no obstruction of the ducts.

Each kidney weighed 175 Gm. and measured 11.5 by 5.5 by 4 cm. The capsules contained small areas of yellow tissue and stripped with ease, leaving a smooth surface which showed dilated veins and patchy areas with a hemorrhagic appearance. There were other areas that were yellow, but these were not sharply demarcated from the surrounding renal tissue.

On the cut surface the pyramids were normal, but the cortex showed yellow areas and surrounding hyperemia and hemorrhage. The cortex was not thickened, measuring 6 mm. The changes involved the columns of Bertin. The pelvis was not remarkable. Microscopic examination revealed large areas of necrosis involving tubules and glomeruli and showing both hyperemia and hemorrhage. Surrounding these was evidence of moderate polymorphonuclear reaction. The areas between the necrotic portions were not abnormal. The arteries also showed necrosis of their walls and some thrombosis. This involved nearly all the arteries seen in the areas of necrosis.

CASE 3.—J. B., a 24 year old man, entered the Cleveland City Hospital on May 21, 1937, with a complaint of vomiting. He had been in good health until five days before admission to the hospital, when generalized abdominal cramps

developed. The following day nausea and vomiting developed, and on one occasion he vomited some digested blood. The day before entry he passed a tarry stool. A little urine had been voided, but the exact amount was not known. The patient was a chronic alcoholic addict but supposedly had not had any liquor for several months.

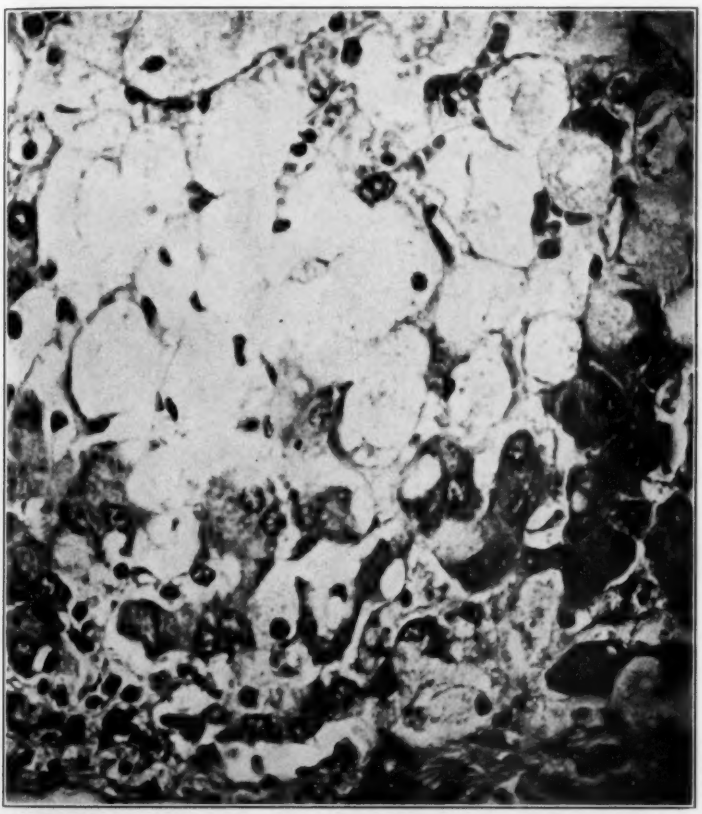

Fig. 1 (case 3).—Central necrosis, the "ghost" appearance of the parenchymal cells and the early degenerative changes in the peripheral zones of the liver are shown. There is an absence of any evidence of cellular reaction; × 600.

Examination showed a well nourished, normally developed semicomatose man. He was obviously seriously ill. The optic disks were edematous. The lungs and heart were normal. The blood pressure was 160 systolic and 88 diastolic. The edge of the liver was palpable 5 cm. below the costal margin. The skin was not icteric.

The leukocytes numbered 45,000 per cubic millimeter. Differential counts showed 95 per cent polymorphonuclear neutrophils and 5 per cent lymphocytes.

Catheterization yielded 2 cc. of urine. Microscopically the uncentrifuged specimen showed a moderate number of granular and hyaline casts, occasional red blood cells and 20 to 30 white blood cells per high power field. The value for urea nitrogen was 246.1 mg. per hundred cubic centimeters of blood; the value for creatinine was 14.5 mg. The reaction to the benzidine test for blood in the stools was 4 plus. The Kline test of the blood gave a negative reaction.

The patient rapidly became comatose; he remained anuric and died ten hours after admission to the hospital.

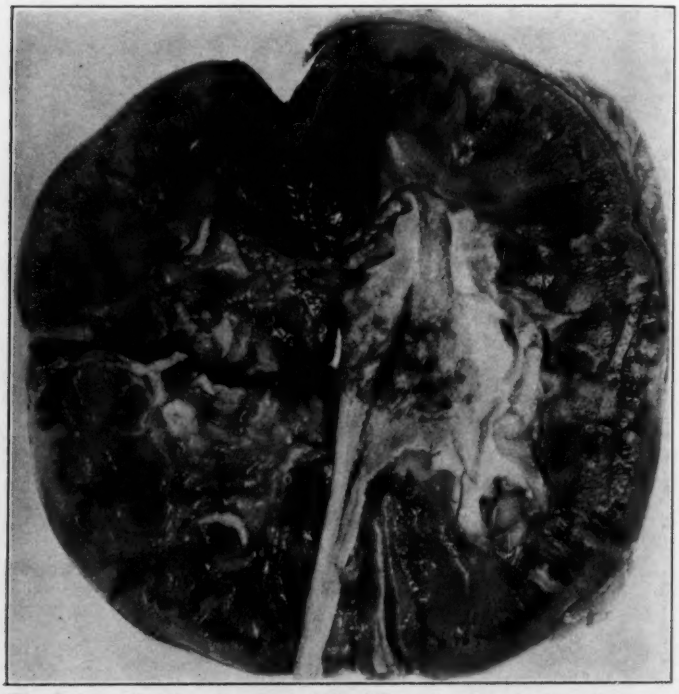

Fig. 2 (case 3).—A cut surface of the kidney showing the irregular necrosis of the entire cortex extending into the columns of Bertin. The hemorrhagic zone sharply demarcates the cortex from the pyramids. The pelvic mucosa shows small hemorrhages.

The clinical diagnosis was uremia of undetermined origin.

The autopsy was performed five hours after death. The body was that of a well nourished man whose external features were not remarkable. There was no peripheral edema.

There was 500 cc. of serous fluid in the peritoneal cavity but no pleural or pericardial effusion.

The lungs showed aspirated blood distributed in symmetric band-shaped zones throughout the subapical regions.

The liver weighed 2,250 Gm. The edges extended 5 cm. below the costal margin in the midclavicular line and were rounded. The capsule was thin, smooth and glistening except for a few fibrous tags on the superior and anterior surfaces. The liver was moderately soft, and it cut with decreased resistance. The cut surface bulged but was not greasy or bloody. The central lobular areas were

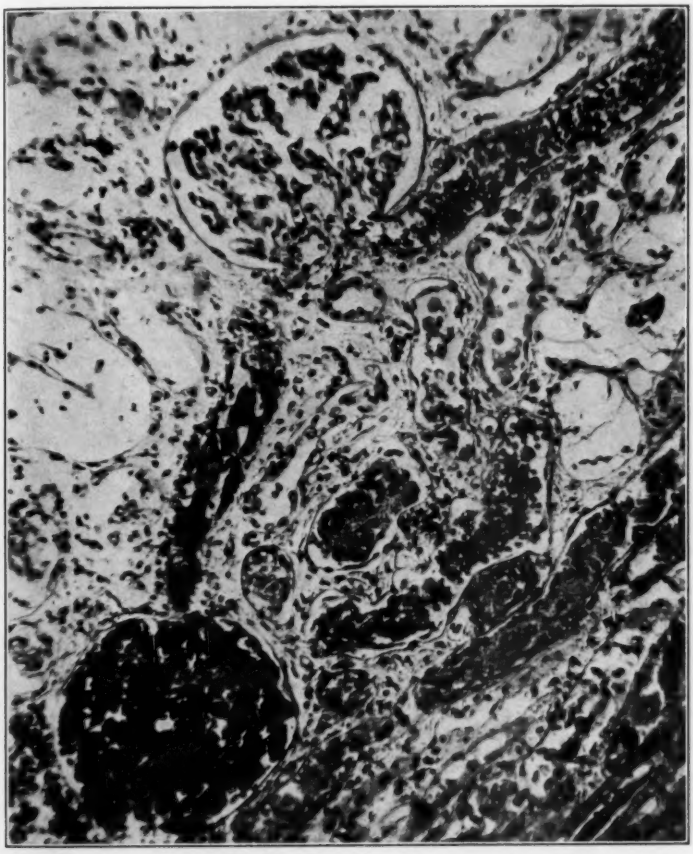

Fig. 3 (case 3).—Complete degeneration of a glomerulus and thrombosis of the afferent arteriole. The section also contains a normal glomerulus; × 350.

reddish brown and depressed, whereas the peripheral areas were grayish yellow and elevated. Microscopic examination revealed the same features as those seen in the first 2 cases, namely, severe central necrosis without evidence of cellular reaction (fig. 1). Staining revealed the absence of both fat and glycogen in the areas of necrosis.

The kidneys were similar. Each weighed 200 Gm. and measured 12 by 6 by 4.5 cm. The capsule was thickened, and it stripped with slight difficulty. Within

the capsule were dilated veins and small irregular hemorrhages. The surface of the kidney was smooth. The color varied; there were areas, irregular in shape, that were dark purple and hemorrhagic, surrounded by areas that were yellow and homogeneous. They were not sharply demarcated, and they faded into each other. The organ cut with the usual resistance, and the cut surface bulged considerably. The cortex and the pyramids were sharply demarcated; the former

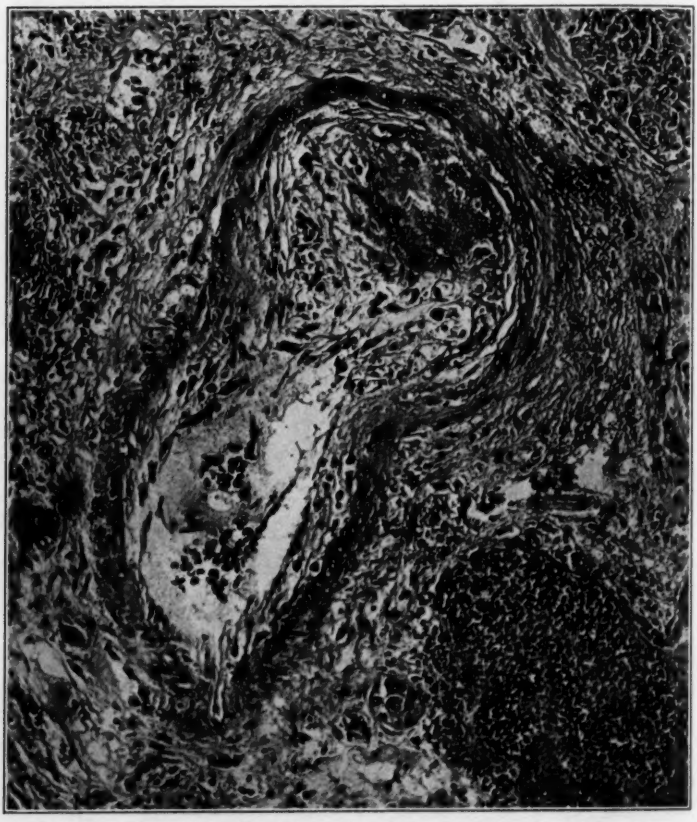

Fig. 4 (case 3).—Necrosis of the wall and an organizing thrombus of a renal interlobular artery; × 250.

measured 6 mm. in thickness and the latter 20 mm. This was accentuated by two factors: first, the light color of the cortex, which varied from tan to bright yellow, and, second, by the narrow, dark, hemorrhagic zone which followed the border of the cortex and the pyramids. The changes in the cortex involved the columns of Bertin and obscured the usual architecture. The changes in the cortex were not uniform. The yellow tissue was homogeneous, and the pinpoint areas representing glomeruli could not be made out. There were irregularly placed

patchy areas of hemorrhagic appearance. The zone of hemorrhage along the corticopyramidal border varied from 1 to 4 mm. in thickness. The pyramids were not unusual. The pelvic mucosa showed numerous small hemorrhages (fig. 2). Microscopic examination revealed small hemorrhages in the capsule with polymorphonuclear infiltration. This infiltration bordered the periphery of the cortex, both near the capsule and near the pyramids. The cortex itself showed complete loss of cellular structure, so that only the "ghosts" of the cells remained and involved both the glomeruli and the tubules (fig. 3). There was a narrow zone near the pyramids wherein the glomeruli showed much less pathologic involvement, but they were few. In the zone of hemorrhage the arteries showed necrosis of their walls and conglutination of red blood cells in their lumens (fig. 4). About half the arteries showed varying degrees of thrombosis. Staining revealed no fat or glycogen in the cortex.

The stomach showed the typical mosaic pattern consistent with chronic hypertrophic gastritis.

The gastrointestinal tract was filled with fresh clotted blood. Bleeding points were searched for carefully, and no explanation for the hemorrhage could be found.

The brain showed slight cerebral edema.

The other organs were essentially normal.

SUMMARY

The pathology, etiology and clinical features of bilateral cortical necrosis of the kidneys are discussed briefly.

Three cases of bilateral cortical necrosis of the kidneys in which autopsy was performed are reported.

These cases are of particular interest because the condition was not associated with pregnancy and because it was associated with central necrosis of the liver.

Central necrosis of the liver associated with bilateral cortical necrosis of the kidneys has been described especially in cases of dioxane poisoning. In the cases reported the condition may have been due to dioxane poisoning, but there was no proof of this; hence, the etiologic factor in these cases is unknown.

Dr. Howard T. Karsner, Professor of Pathology, Western Reserve University, assisted in preparing the photomicrographs and criticized the manuscript.

INSULIN RESISTANCE

REPORT OF A CASE OF MARKED INSENSITIVENESS OF LONG DURATION WITHOUT DEMONSTRABLE CAUSE

ALEXANDER MARBLE, M.D.
BOSTON

Since July 1935 my colleagues and I have had the opportunity of observing a diabetic patient with crippling although afebrile rheumatoid arthritis who has required from 240 to 675 units of insulin daily for control of hyperglycemia and glycosuria. The situation is so extraordinary that certain special studies have been made which are reported in the present communication. Although one sees patients occasionally who require large quantities of insulin, almost invariably a responsible complication can be disclosed, and, even so, the total daily dose rarely exceeds 100 units. The case to be described is without parallel in a group of approximately 11,500 patients with true diabetes seen in this clinic since the introduction of insulin in 1922. The only other patient in our series with an enormous insulin requirement was a doctor with hemochromatosis, previously reported on,[1] who died in coma despite a final dosage of 1,680 units of insulin a day. His case differed materially from that of the woman under discussion, however, in that the course was rapidly progressive and the insulin resistance was satisfactorily explained by the complicating hemochromatosis.

REPORT OF CASE

Mrs. Helen St. C., of French-Canadian parentage, a former nurse, was admitted to the New England Deaconess Hospital on July 2, 1935. She had been transferred from a hospital in a neighboring city.

I. *First Hospitalization* (July 2, 1935 to April 29, 1936).—Family History: The patient's father was living at the age of 75 and was well except that he had complained of arthritis since the preceding winter. Her mother was living and well at 65 years of age. There were five brothers, aged 20 to 37 years, and five sisters, aged 19 to 39 years, who were living and well. Five uncles and aunts were living and well. There was no history of arthritis or diabetes in the family other than as previously mentioned.

From the George F. Baker Clinic, Dr. Elliott P. Joslin, medical director, New England Deaconess Hospital.

The expenses of the studies, other than those of a routine nature, which are reported in this paper were defrayed in part by a grant from the Chemical Foundation, Inc.

1. Root, H. F.: Insulin Resistance and Bronze Diabetes, New England J. Med. **201**:201 (Aug. 1) 1929.

Past History: The patient was born on April 17, 1900, in Ontario, Canada. She was graduated from the nurses' training school of a large general hospital in Toronto, Canada, in 1920 and in 1923 took postgraduate work at a maternity hospital in New York. She continued nursing until about 1931. She lived in New York off and on between 1928 and 1932. Since 1932 she had lived in a city in Massachusetts.

The patient was married in May 1925, a year or two after coming to the United States from Canada. There was one miscarriage in 1926, and in 1931 a son was born who suffered periodic convulsions owing to an injury at birth. The patient's husband was about 45 years of age and had asthma, but there was no history of diabetes in his family.

Operations: The following operations had been carried out: 1922, tonsillectomy; 1926, dilatation and curettage for incomplete miscarriage; 1928, appendectomy, oophorectomy and ventral suspension of the uterus; May 1935, hemorrhoidectomy.

Illnesses: Except for measles in childhood, pneumonia at the age of 19 and attacks of tonsillitis prior to the operation in 1922, the patient had had no noteworthy illnesses.

Present Illness: The first signs of arthritis were noted in 1926, when there was involvement of both shoulders. She noticed the pain at this time chiefly when lying down. She was not ill enough to go to bed and continued at her work of nursing at a hospital in New York. The disability lasted from about the spring to the fall of 1926. Then followed a period of quiescence, and it was not until about October 1932, while she was still in New York, that symptoms of arthritis reappeared. At this time the right elbow was the first joint affected, and after this the feet and ankle joints were involved. The arthritis was at first migratory, and the joints were swollen, red and tender. Rheumatic fever was suspected at the time, but the patient never had fever. During the summer of 1933 the arthritis was severe, and from this time on the patient was actively treated for this disease by doctors in New York and Massachusetts. For the several months prior to April 1935 her condition was poor, and although she was never confined entirely to bed, she was a semi-invalid.

The date of onset of diabetes is difficult to establish. It is true that for an indefinite period the patient had suffered polyuria and polydipsia, but she could remember no time at which there was an increase in thirst or in the quantities of urine voided. She stated that she was in the habit of drinking large amounts of water along with the medicine given to her for arthritis. She recalled that in November 1933, at a visit to her doctor, she weighed 105 pounds (47.6 Kg.) dressed, and it was remarked at the time that she was losing weight. It must be remembered, however, that she was then suffering from chronic arthritis. Unfortunately her physician did not obtain a specimen of urine at that time. It seems fairly certain that in about 1932 the urine was examined and declared free from sugar.

The patient was admitted to a hospital in a city close to Boston on April 22, 1935. Several days before entry her local physician told her that she had "about 10 per cent sugar in the urine." During this hospitalization the patient was much improved and was discharged on June 7. She returned thirty hours later, on June 8, in impending diabetic coma. Because of the fact that her diabetes was difficult to control and because some endocrine disturbance other than the diabetes was suspected, she was transferred to the New England Deaconess Hospital.

Examination: When the patient was admitted to the New England Deaconess Hospital on July 2, 1935, she was seen to be poorly nourished. Her height was 64 inches (162.6 cm.), and her body weight (stripped) was 84¼ pounds (38.5

Kg.). She looked pale. The heart was of normal size and had a regular rhythm, and no murmurs were heard. The lungs were clear, the abdomen was soft and nontender, the spleen was palpable and the kidneys were palpable but not enlarged. The circulation to the feet seemed good. The blood pressure was 100 systolic and 60 diastolic. A Hinton test of the blood gave negative results. The urine on entry contained 1.9 per cent sugar, a negligible amount of albumin and no bile or diacetic acid. The blood sugar content during fasting was 0.25 per cent, and the nonprotein nitrogen content was 28 mg. per hundred cubic centimeters.

Roentgenograms of the chest on July 12 showed the cardiac shadow and the pulmonary markings to be within normal limits. Roentgenograms taken on July 25 showed the bones of the skull to be thick and dense, the pineal gland calcified and the sella turcica normal in size and regular in contour. Pyelograms taken after the intravenous injection of an opaque solution on July 27 revealed hydronephrosis on both sides, with considerable extrarenal dilatation and a sharp kink at the ureteropelvic junction on the right. (The patient had not had nor has she since had any symptoms directly referable to these abnormalities.) The findings as regards the joints will be discussed later.

Course in the Hospital: 1. Diabetes. The patient remained in the hospital until April 29, 1936, about ten months. The course was most extraordinary and is set forth graphically in figure 1. It was soon found that the diabetes was not of the usual type, because at the end of the first week even with a low diet (carbohydrate, 120 Gm.; protein, 56 Gm., and fat, 84 Gm.), making a total of 1,400 calories per day, she excreted in the urine during a typical twenty-four hour period considerable diacetic acid and acetone and 39 Gm. of sugar, although she was receiving a little over 100 units of insulin during the day. Accordingly the dose of insulin was gradually increased in an attempt to control the excretion of sugar. Because of her extreme hunger and our desire to relieve her emaciated condition, the diet was also increased at regular intervals. Accordingly, about a month after entry, with a diet containing 148 Gm. of carbohydrate, 86 Gm. of protein and 107 Gm. of fat, making a total of 1,899 calories per day, she was receiving 196 units of insulin. She still showed a yellow, red or orange reaction to the Benedict test for sugar throughout the day. On October 23 she was given 530 units of insulin in six doses. By November 2, four months after entry, she was receiving 475 units of insulin a day, and this was with a liberal diet (carbohydrate, 200 Gm.; protein, 112 Gm., and fat, 141 Gm., making a total of 2,570 calories per day). The urine was by no means free from sugar, however. In order to test the influence of the amount of carbohydrate in the diet on the insulin dosage, this was gradually reduced to 120 Gm. a day. It was found, however, that such a reduction did not materially decrease the amount of insulin required, and even with 120 Gm. of carbohydrate, 107 Gm. of protein and 143 Gm. of fat (2,197 calories a day), she required 470 units of insulin (fig. 1). It was demonstrated by lengthy trials that the type of insulin was not a factor; the patient was given pure beef insulin, beef and pork insulin, pure pork insulin and crystalline insulin.[2] Different brands were tried, but no difference was noted.

It was repeatedly demonstrated during this and subsequent hospitalization that failure to supply sufficient insulin resulted in a prompt flareup of hyperglycemia and glycosuria. Contrariwise, when too much insulin was given, typical hypoglycemic symptoms resulted. In other words, this patient reacted to treatment

2. The crystalline insulin was supplied by Prof. C. H. Best, of the University of Toronto, and the special pork insulin by Eli Lilly & Co.

as does the patient with straightforward diabetes except that the amount of insulin required for control was roughly ten times that required by the average patient with moderately severe diabetes.

On January 4, because of marked induration of the skin and atrophy of the subcutaneous fat over the thighs, due to repeated injections of large amounts of insulin, the site of administration was changed to the abdominal wall. The consequences of this were unexpected and most extraordinary. At about 10 p. m. the patient noted symptoms of hypoglycemia; the blood sugar value at that time

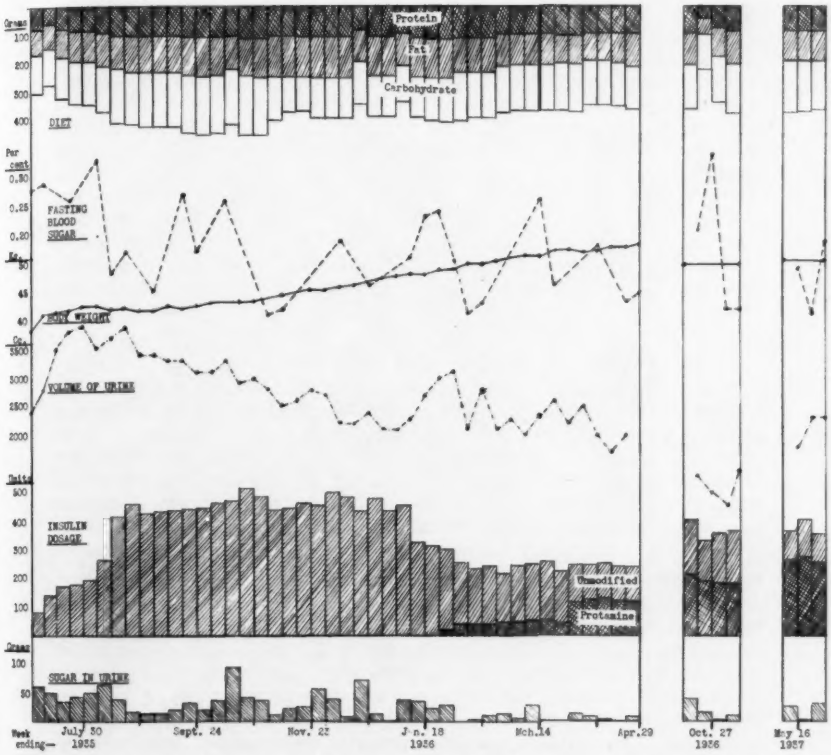

Fig. 1.—A chart summarizing the data obtained during the course of the patient's three periods of hospitalization. Each block on the chart gives average values for one week.

was found to be 0.04 per cent. Orange juice gave relief, and the patient slept the rest of the night, but at 6 a. m. she awakened with severe headache in the occipital region of the type experienced in prolonged though not severe hypoglycemia. The blood sugar value at 7:30 a. m. was 0.07 per cent. Because of this the dose of insulin was lowered and after a few days of adjustment was stabilized at a level of 300 to 340 units a day, approximately 100 units lower than before the site of injection was changed.

This effect was so striking that on February 1 the site was again changed, this time to an entirely fresh area on the flanks. Before the change the daily dose averaged 300 units. With continuance of injection of this amount in the fresh area, again prolonged hypoglycemia was produced, and after a few days of adjustment a new total of 240 to 260 units was found adequate.

This experience demonstrated anew and conclusively the value of insisting that the diabetic patient change the site of injection from one time to the next so that no one spot receives insulin oftener than every three or four weeks. Only in this way can the full value of the insulin be uniformly secured. Effects such as those secured in this case ordinarily pass unnoticed because of the differences in doses involved, changes being evident in the average case on a scale only one-tenth as great.

On January 23 the first dose of protamine insulin (Danish)[3] was administered to this patient. It was given simply as a supplementary dose of 20 units at 10 a. m. As time went on, bolder use was made of it by gradual stages; finally, on April 7, simply 120 units of regular (unmodified) insulin plus 120 units of protamine insulin (Danish) was given in two injections at one time in the morning before breakfast, and then no more insulin was given during the rest of the day. The results far exceeded our expectations. Instead of six injections of regular insulin daily as before, the diabetic condition was then under good control with insulin administered only once a day. On the morning before her discharge, the blood sugar content during fasting was normal, 0.10 per cent. On discharge (April 29) the patient was instructed to take 120 units of unmodified and 120 units of protamine insulin (Danish)[4] each morning.

2. Glandular enlargement. On Sept. 12, 1935, it was noted for the first time that the patient had general glandular enlargement involving the cervical, axillary, epitrochlear and inguinal regions but most marked in the last-named location, so much so that she had a great deal of pain in the groins, particularly on the right. This glandular enlargement persisted to a marked degree until April 1936. Histologic examination of a node taken from the left axilla showed only chronic inflammation. The liver and spleen were always palpable. Roentgenograms revealed no mediastinal nodes or calcified abdominal nodes. Because of the splenomegaly, arthritis and leukopenia, the diagnosis of Felty's[5] syndrome was at one time considered.

3. Arthritis. The chief articular involvement at first was that of the knees and elbows, which during the first six months of hospitalization were markedly swollen, distended with fluid, somewhat tender to touch and painful on motion. To some extent the ankles, hips, shoulders and joints of the fingers and toes were affected. Later the right ankle was the chief joint involved. A surprising characteristic was the lack of limitation of motion, considering the amount of involvement. Roentgenograms of the various joints showed in most cases that the surfaces were well preserved, with little or no erosion of the bone or cartilage (figs. 2 to 4). Acute exacerbations of the arthritis (with little or no fever, however) were experienced at occasional intervals during the first six months,

3. Obtained through Dr. H. C. Hagedorn, of the Steno Memorial Hospital, Copenhagen, Denmark.

4. To be comparable to the American preparations of protamine insulin that were used later, all doses of the Danish variety should be multiplied by eleven-fifteenths.

5. Felty, A. R.: Chronic Arthritis in the Adult, Associated with Splenomegaly and Leukopenia, Bull. Johns Hopkins Hosp. **35**:16 (Jan.) 1924.

but the general tendency was toward improvement; and at the time of discharge (April 29) there was little or no fluid in any of the joints, and motion everywhere was remarkably free, although of course there was well marked generalized deformity, with crepitus easily audible, particularly in the knee joints.

Treatment for the arthritis consisted of prolonged rest at first, followed by gradually increasing exercise, passive motion and massage and the use of contrast baths, radiant heat and analgesics.

4. Hematologic findings. When the patient was admitted to the hospital the erythrocyte count was 4,510,000, and the hemoglobin value was 70 per cent (Sahli). During the next three weeks the values fell to a level of 3,900,000 and 63 per cent, respectively, presumably because of the retention of fluid in the body and relief of dehydration of the tissues. During the ensuing weeks and months, coincident with the giving of ferrous sulfate orally in doses of 12 grains (0.78 Gm.) daily,

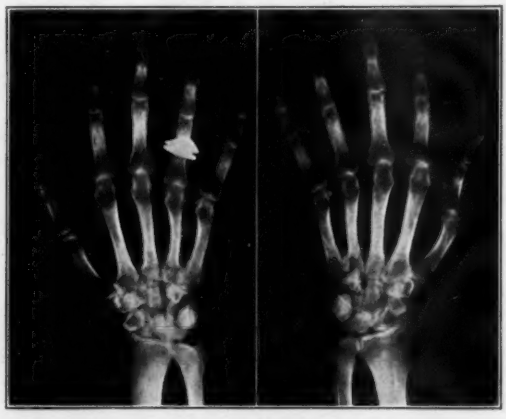

Fig. 2.—Roentgenograms of the hands showing arthritic changes, with narrowing of the articular spaces and swelling of the soft parts. Note also rarefaction of the bone at the ends of the metacarpal bones and the phalanges.

the anemia gradually disappeared, and during the last four months of hospitalization the red blood counts varied between 4,410,000 and 4,980,000 and the hemoglobin values between 80 to 96 per cent.

Prior to her entry (July 2, 1935) the white blood cell count obtained elsewhere had varied from 3,800 to 4,700. The first count at the New England Deaconess Hospital gave a value of 7,050, and no figure below 5,800 was obtained until August 1. From this time until September 2 the counts varied from 3,900 to 5,450. During the subsequent eight months the values were within normal limits, ranging from 5,600 to 11,600 but usually from about 7,000 to about 8,500.

The most striking hematologic finding was that of eosinophilia. Studies elsewhere just prior to entrance showed only 2 per cent eosinophils, and the blood smear made on entry showed this same value. On August 26, however, 15 per cent eosinophils was noted, and from then on abnormally high values were the rule. The highest percentages were 31 on September 27, 36 on November 13, 33 on January 14, and 33 on April 8. In the absence of any other cause, it seems

reasonable to conclude that the eosinophilia was part of an allergic response provoked by the extremely large doses of insulin. Such a finding has been reported by Lawrence [6] and Lawrence and Buckley.[7]

5. Disease of the endocrine glands other than the pancreas. Because in the earlier part of the patient's stay in the hospital the basal metabolic rate was regularly found to be +25 or +26 per cent, hyperthyroidism was considered as a diagnosis. However, with only rest in bed and no specific therapy, the basal metabolic rate gradually fell so that the last determination of a given series was +7 per cent, and on Oct. 17, 1936, it was +1 per cent. The iodine content of blood taken with the patient in the fasting state (2 micrograms per hundred cubic centimeters of blood), when considered in connection with a normal blood iodine curve after the giving of 50 mg. of iodine by mouth, did not suggest

Fig. 3.—Roentgenograms of the knees, showing arthritic changes, with narrowing of the articular spaces, swelling of the soft parts and generalized rarefaction of bone.

hyperthyroidism.[8] Her creatine tolerance was found to be low; after receiving 1 Gm. of creatine by mouth, she excreted 60 per cent of it in the urine within twenty-four hours. Although this is compatible with hyperthyroidism, it is not pathognomonic and might well be a finding in any chronic wasting disease.

It is of interest that in March 1936 the patient began menstruating for the first time in ten months.

Roentgenograms of the skull showed no enlargement of the sella turcica, and examination of the eyegrounds revealed no abnormality. There was nothing other than the insulin resistance which suggested pituitary disease. In the hope

6. Lawrence, R. D.: Studies of an Insulin Resistant Diabetic, Quart. J. Med. **21**:359 (April) 1928.

7. Lawrence, R. D., and Buckley, O. B.: Eosinophilia in Insulin Therapy, Brit. M. J. **1**:597 (March 30) 1929.

8. These studies were carried out under the direction of Mr. H. J. Perkin, of the Lahey Clinic.

of demonstrating the presence in the blood of some substance possessing hyperglycemic or diabetogenic activity, 5 to 5.5 cc. of (fasting) blood serum from the patient was injected intravenously into a 3,720 Gm. white male rabbit on three successive days, and on the third day 7.4 cc. of 50 per cent dextrose was administered intravenously (with the rabbit in the postabsorptive state) two hours after the giving of the patient's serum. Serial determinations of the blood sugar content were then made at frequent intervals for over three hours. The results were conclusively negative, in that the dextrose tolerance curve obtained differed

Fig. 4.—Anterior view of the legs, showing arthritic deformity at the knees and areas of atrophy of subcutaneous fat over the thighs.

in no significant detail from two control curves previously obtained for the same rabbit (using a comparable technic but without the injection of the patient's serum). It would be of interest to know whether or not injection of this patient's serum into a rabbit would modify the curve obtained after the injection of a suitable dose of insulin. With this procedure an antagonistic effect has been observed by de Wesselow and Griffiths,[9] particularly with blood serum of elderly, obese diabetic patients, but in our own limited experience we have been unable to corroborate these findings.

9. de Wesselow, O. L. V., and Griffiths, W. J.: On the Possible Role of the Anterior Pituitary in Human Diabetes, Lancet **1**:991 (May 2) 1936.

6. Other features. No infection other than arthritis was demonstrated. Roentgenograms of the chest showed no evidence of tuberculosis. A biopsy of the skin showed no hemosiderin, nor did at least three examinations of the urinary sediment by the method of Rous [10] give any support to the diagnosis of hemochromatosis. Tests for Bence Jones protein in the urine repeatedly gave negative results. The chloride and uric acid contents of the blood serum were normal, and the total cholesterol content of the plasma was low normal, varying from 125 to 136 mg. per hundred cubic centimeters. One determination of the gastric contents showed no free hydrochloric acid, and this was confirmed by fractional aspiration after a test meal of 100 cc. of 7 per cent alcohol, samples being taken during fasting and at intervals of fifteen minutes for an hour after the test meal.

Excretion of Nitrogen in the Urine

	Urine, 24 Hour Amount			Diet	
		Total Nitrogen		Protein (Calculated),	Nitrogen (Average),
Date	Volume, Cc.	Gm. per Day	Average, Gm.	Gm.	Gm.
1935					
Aug. 13-14	3,600	12.5		102	
14-15	4,300	13.9		102	
15-16	3,600	15.4	13.9	108	16.3
Oct. 22-23	2,100	11.4		112	
23-24	2,600	11.8		112	
24-25	3,185	14.9	12.7	112	17.9
Nov. 20-21*	2,300	19.1		107	
21-22	2,700	16.7		107	
22-23	2,300	13.3	16.4	107	17.1
1936					
April 17-18	1,630	11.9		96	
18-19	1,750	9.3		96	
19-20	1,850	10.1	10.4	96	15.4

* In retrospect it is difficult to explain the variation in results obtained during the three days in November. Unfortunately no creatinine values are available as a check on the accuracy of the collections of urine.

The phenolsulfonphthalein test of renal function gave normal results, with an excretion of 60 per cent of the dye in two hours and ten minutes. The bromsulphalein test of hepatic function showed normal clearance of the dye from the blood stream. Of twelve tests for urobilinogen (scattered over a period of months) in twenty-four hour specimens of urine, two were reported as showing a positive result in 1 : 10 dilution, two in 1 : 20, four in 1 : 30, three in 1 : 50 and one (faintly) in 1 :100. Since the results of the test (method of Wallace and Diamond [11]) are regarded as abnormal if a positive reaction is obtained in dilutions over 1 :20, there was some suggestion of hepatic impairment in this case.

The total nitrogen content of the urine on representative days is shown in the accompanying table. The figures indicate a greater or less degree of nitrogen

10. Rous, P.: Urinary Siderosis: Hemosiderin Granules in the Urine as an Aid in the Diagnosis of Pernicious Anemia, Hemochromatosis, and Other Diseases Causing Siderosis of the Kidney, J. Exper. Med. **28**:645 (Nov.) 1918.

11. Wallace, G. B., and Diamond, J. S.: The Significance of Urobilinogen in the Urine as a Test for Liver Function, Arch. Int. Med. **35**:698 (June) 1925.

retention. This might be expected, since during this period the body weight and strength had been steadily increasing. Values for ammonia nitrogen in the urine were found in April 1936 to vary from 0.37 to 0.58 Gm. per twenty-four hours, or from 3.9 to 4.9 per cent of the corresponding values for total nitrogen.

At discharge the patient weighed 117¼ pounds (53.3 Kg.), or 32½ pounds (14.8 Kg.) more than on entry ten months previously! This attests as much as anything else to her great improvement during this period.

II. *Second Hospitalization* (Oct. 13 to Nov. 8, 1936).—The patient was readmitted to the hospital on Oct. 13, 1936, for further study. During the five and one-half months at home she had been in fair condition although handicapped greatly by arthritis. With the aid of crutches she had been able to be up and around for part of each day. She complained of nervousness and irritability and of painful bleeding hemorrhoids. Although at the time of entry the dose of insulin was 150 to 200 units of regular (unmodified) insulin and 240 units of protamine insulin (Danish) once daily in the morning before breakfast, she had taken during the summer as much as 400 units of unmodified insulin and 275 units of protamine insulin (total 675 units) a day. She had kept her diet at a level of 150 Gm. of carbohydrate, 100 Gm. of protein and 110 Gm. of fat a day. Menstrual periods had been occurring every three weeks, lasting usually for six or seven days, with excessive flowing for three days of that time.

On physical examination the heart and lungs were found to be essentially normal, and the blood pressure was 95 systolic and 60 diastolic. The liver could be felt to descend 3 cm. below the costal margin in the mamillary line, and the spleen could be felt to descend 1 to 2 cm. A few small cervical, practically no axillary, one small right epitrochlear and several inguinal nodes on each side could be felt. Even the last-named glands, however, were appreciably smaller than on the first entry. One right inguinal node was slightly tender. There were subcutaneous lumps over the thighs and abdomen at the sites of injections of insulin. Pelvic examination indicated an essentially normal condition. The urine contained no albumin. The erythrocytes numbered 4,470,000 and the white blood cells 7,450 per cubic millimeter. The hemoglobin value was 85 per cent; a blood smear showed: neutrophils, 44 per cent; lymphocytes, 33 per cent, and eosinophils, 23 per cent. The basal metabolic rate was +1 per cent.

On October 20 incision and curettage of an anal fissure and dilatation of the anal sphincter were carried out by Dr. T. C. Pratt, with the patient under spinal anesthesia. The postoperative course was uneventful. Incidentally, spinal fluid removed just before the operation gave a negative reaction to the Wassermann test; microscopic examination of the undiluted fluid in a counting chamber showed only 2 cells in the entire field.

During her stay in the hospital the patient's diet contained 167 Gm. of carbohydrate, 84 Gm. of protein and 115 Gm. of fat. The diabetic condition was kept under control with 180 units of unmodified and 180 units of protamine insulin (Squibb) daily, simultaneous doses being given before breakfast (fig. 1).

At this time it was found that the capsular tissue of both knee joints was loose, apparently because of the absorption of the long-standing effusion which had in the past caused much stretching. Hence inadequate support was available, and there was a marked tendency for the patient's legs to give way when she attempted to walk. This was partly corrected by making a brace for the left knee.

III. *Third Hospitalization* (May 9 to 30, 1937).—The patient again entered the hospital on May 9, 1937, for a stay of three weeks. During the six months since her second entry she had improved in strength, and she looked better in

general. There had been no acute exacerbation of arthritis, although her activity was still markedly limited because of articular pain. She had taken from 280 to 430 units of insulin daily. The findings on physical examination did not differ greatly from those at the last entry, although there was if anything less activity as regards the arthritic process, the general glandular enlargement was less striking and the spleen could not be felt. There was no anemia, the white blood cell count varied from 6,300 to 9,400 and the percentage of eosinophils varied from 5 to 12. The body weight was 110 to 111 pounds (50 Kg.). On discharge the patient was advised to follow a diet calling for 167 Gm. carbohydrate, 84 Gm. of protein and 130 Gm. of fat daily and to take 100 units of unmodified insulin and 300 units of protamine zinc insulin daily at one time in the morning before breakfast.

During this stay in the hospital, through the cooperation of Dr. J. H. Marks, roentgenologist, six irradiations of the skull (hypophysial region) were given, one each day for six consecutive days (May 24 to 29, 1937; a total of 1,200 roentgens [400 kilovolts] over a field [6 by 6 cm.] in each temporal region). No alteration of the insulin requirement was noted then or subsequently.[11a] This experience is contrary to that reported by Merle,[12] Pieri and Sarradon[13] and Cannavo.[14]

COMMENT

In certain of the cases of marked resistance or refractoriness to insulin reported in the literature, some factor has been apparent to which it seemed reasonable to assign the responsibility for the condition. Thus the patient reported on by Altshuler and Gould[15] was found post mortem to have a large suprasellar cystic hematoma which pressed on the optic chiasm, hypophysis and neighboring structures. In Wayburn's[16] case there was extensive pulmonary tuberculosis, in Warvel's[17] a pineal tumor and in Engel's[18] and Root's[1] hemochromatosis. In other instances no cause has been apparent. In the case reported by

11a. Note added on June 30, 1938: Since this paper was submitted for publication a further attempt has been made to demonstrate an influence from irradiation of the skull. From April 13 to 27, 1938, twelve irradiations of 300 roentgens each were given over a field 4 cm. in diameter in each temporal region at a distance of 50 cm., a total of 3,600 roentgens (200 kilovolts). No significant effect on the diabetic condition or on the insulin requirement has been noted.

12. Merle, E.: Diabète grave insulino-résistant: Réduction brusque et massive de l'insulino-résistnace par irradiation de la région hypophysaire, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:35 (Jan. 21) 1935.

13. Pieri, J., and Sarradon, P.: Diabète grave insulino-résistant: Réduction notable de l'insulino-résistance par la radiothérapie hypophysaire, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1579 (Dec. 2) 1935.

14. Cannavo, L.: Insulinoresistenza e irradiazioni röntgen della regione ipofisaria, Policlinico (sez. prat.) **43**:1099 (June 15) 1936; abstracted, J. A. M. A. **107**:545 (Aug. 15) 1936.

15. Altshuler, S. S., and Gould, S. E.: Diabetes Refractory to Insulin, with Report of a Case, Ann. Int. Med. **9**:1595 (May) 1936.

16. Wayburn, E.: Complete Insulin Resistance in Diabetes, Am. J. M. Sc. **190**:157 (Aug.) 1935.

17. Warvel, J. H.: Personal communication to the author.

18. Engel, R.: Insulinrefraktärer Diabetes bei schwerem Leberschaden, Klin. Wchnschr. **13**:1682 (Nov. 24) 1934.

Clay and Lawrence [19] there was found at postmortem examination no adequate explanation for the unusual requirement of insulin, which reached 960 units during the last twenty-four hours of life. It is true that this 63 year old man had pernicious anemia (controlled) and heart disease in addition to diabetes. Mason and Sly [20] concluded that the resistance of their patient was due to a "marked lessening of the liver's ability to convert dextrose to glycogen or an intermediate product in this conversion." In their patient, a 25 month old boy, glycosuria could be almost stopped by the substitution of levulose or galactose for dextrose in the diet. Unfortunately no postmortem examination was allowed in the extraordinary case reported by Thannhauser and Fuld,[21] in which, despite large amounts of insulin (200 to 240 units a day) for several days and 1,230 units (170 units subcutaneously and 1,060 units intravenously) on the final day, death took place in coma.

Reviews of the subject from different approaches are to be found in the papers by Falta and Boller,[22] Pollack [23] and Aubertin.[24]

The cause of the extraordinary insensitiveness to insulin exhibited by the patient reported on in the present paper is an interesting problem. The following possibilities suggest themselves:

1. Hemochromatosis. Against this diagnosis were the absence of the characteristic color of the skin and the negative results of tests for iron pigment in the skin at biopsy and in the cells of the urinary sediment. Moreover, as time has gone on, the patient's general condition has improved (it has not become progressively worse, as in our other case, reported on by Root [1]), and the enlargement of the liver and spleen, never great, has become less.

2. Infection. The only significant infection which has been demonstrated in this patient is that of rheumatoid arthritis. However, only occasionally has there been enough activity to cause fever, and, even then, various consultants, specialists in orthopedic and arthritic disorders, have agreed that this infectious process was in no way adequate to account for the startlingly high requirement of insulin. Furthermore,

19. Clay, P. D., and Lawrence, R. D.: Insulin Resistance, Brit. M. J. **1**:697 (April 6) 1935.

20. Mason, H. H., and Sly, G. E.: Diabetes Mellitus: Report of a Case Resistant to Insulin But Responsive to a Change in the Type of Carbohydrate Fed, J. A. M. A. **108**:2016 (June 12) 1937.

21. Thannhauser, S. J., and Fuld, H.: Insulinmangelkoma und Insulinrefraktäres Koma im Verlaufe eines Diabetes mellitus, Klin. Wchnschr. **12**:252 (Feb. 18) 1933.

22. Falta, W., and Boller, R.: Insulärer und Insulinresistenter Diabetes, Klin. Wchnschr. **10**:438 (March 7) 1931.

23. Pollack, H.: Conditions Associated with Unusual Requirements for Insulin, Proc. Staff Meet., Mayo. Clin. **8**:453 (July 26) 1933.

24. Aubertin, E.: L'insulinorésistance, Bruxelles-méd. **16**:453 (Jan. 26) 1936.

during the past year, while the arthritic process has been relatively quiescent, the large doses of insulin have had to be continued.

Physical examination and roentgenograms have given no evidence of pulmonary tuberculosis. Wayburn [16] said he regarded this condition as responsible for the extraordinarily large requirement of insulin in the case reported by him.

3. Disorders of the endocrine glands other than the pancreas. As far as possible pituitary disease has been excluded as a cause, although the means available today are admittedly inadequate to show functional disorders. Roentgenograms have shown the sella turcica to be normal, examination has always shown the eyegrounds to be normal and irradiation of the skull daily for six days produced no effect on the requirement for insulin. The moderate elevation of the basal metabolic rate obtained in earlier observations brought up the question of overactivity of the thyroid gland, but clinical findings and other laboratory tests have not been consistent with this diagnosis; later determinations of the basal metabolic rate have given normal results. The normal blood pressure and the absence of signs of Cushing's syndrome are against dysfunction of the adrenal glands. Roentgenograms of the skull have shown calcification in the region of the pineal gland, but this is so frequently seen in roentgenograms that its significance is questionable. The possibility of a disturbance in this organ was thought of because of Warvel's [17] remarkable case of a girl who received extraordinarily large amounts of insulin over a period of ten months and at postmortem examination (after death in diabetic coma) was found to have a pineal tumor. Related ovarian dysfunction was evident in our own patient in view of the fact that she did not menstruate from May 1935 to March 1936, but the amenorrhea was undoubtedly an effect rather than a cause.

4. Extensive pancreatic disease—structural or functional. It is conceivable that marked destruction of the islet-containing tissue of the pancreas might cause diabetes with a large requirement of insulin for its control. In our patient no sign of a tumor or of inflammatory disease of the pancreas has appeared. Furthermore, the amount of insulin necessary to control hyperglycemia and glycosuria is larger than that which Root [1] said he regarded as the requirement of a completely depancreatized man, namely, 200 to 300 units daily. Although the evidence is wholly indirect, it is entirely possible that the pancreas of our patient secretes an amount of insulin approaching the normal and that the chief abnormality is due to extrainsular influences.

5. Miscellaneous conditions. Diabetic acidosis or coma, which temporarily almost invariably calls for an increased amount of insulin, has obviously not been a factor in our case. Also there has been no suggestion of cardiac decompensation.[22]

6. As regards many obscure metabolic problems, one invariably turns to the liver in searching for an explanation of phenomena observed. The liver is a great transforming agent not only of carbohydrate but also of protein and fat, storing, yielding up or modifying these substances as bodily needs arise. One of the characteristics of diabetes mellitus is the inability of the body to maintain normal stores of glycogen in the liver. Instead, dextrose floods the blood and body tissues generally. Furthermore, possibly as a result of hypophysial action and possibly also by virtue of the mediation of the adrenal cortex,[25] dextrose is formed in excessive amounts from noncarbohydrate sources. Insulin in proper doses corrects these abnormalities, as well as promotes normal utilization of dextrose in the tissues. It is possible that in our patient glycogenolysis and the new formation of sugar from protein and fat proceed with such ease and the opposite chemical changes proceed with such difficulty, possibly because of hormonal influences, such as those from the pituitary body or the adrenal cortex, that enormous amounts of insulin are necessary to main the proper balance. We do not know to what extent, if any, in our patient utilization of dextrose in the tissues proceeds less normally than in the usual diabetic patient.

Other possibilities are that there exists in the blood and tissues some agent which in a more direct way than has been suggested may oppose or neutralize the action of insulin [26] or that some enzyme needed for the activation of insulin, such as an "insulin-kinase," [27] is deficient because of a defect of the pancreas or of the liver. These possibilities, although interesting, find no support in concrete data. Furthermore, somewhat rough tests (assay in mice) have not supported the possibility that the huge amounts of insulin given our patient are in large part excreted in the urine.

The patient is being kept under close observation in the hope that the solution of her problem may throw light on the problem of diabetes in general.

SUMMARY

A report is made of a patient with marked insensitiveness to insulin who has been observed closely since July 1935. This woman (who was 35 years of age when first seen) has chronic rheumatoid arthritis. The insulin requirement has varied from 240 to 675 units daily.

25. Long, C. N. H.: The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, pp. 194-228.

26. Fitz, R.: Does Diabetic Blood Contain an Insulin-Inactivating Substance? in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 446.

27. Himsworth, H. P.: The Activation of Insulin, Lancet **2**:935 (Oct. 29) 1932.

Complications other than the arthritis have included marked general glandular enlargement, slight to moderate hepatomegaly and splenomegaly and eosinophilia of striking degree. The last-named complication has been attributed to the large doses of insulin.

The occurrence of lipodystrophy at the site of the injections of insulin has been a problem.

In a striking way it has been demonstrated that injection of insulin into areas of tumefaction and scarring (produced by multiple previous injections) is less effective in lowering the blood sugar than injection into a normal area.

Control of the diabetic condition has been followed by a gratifying gain in weight and strength.

Attempts to demonstrate a pituitary, adrenal, thyroid or gonadal influence as being responsible for the resistance to insulin have been unsuccessful as far as direct evidence is concerned. Other possible causes for the condition, including hepatic dysfunction and abnormal excretion of injected insulin, are discussed.

NOTE (June 30, 1938).—After the completion of the foregoing report, the patient was studied again during a fourth visit to the hospital, on April 10 to May 4, 1938. There had been no essential change in her condition. Prior to entry she had been taking 100 units of unmodified and 160 units of protamine zinc insulin daily. In the hospital it was possible to reduce for a few days the amount of insulin to a total of 150 units of the unmodified type (no protamine insulin). However, the requirement then rose so that on the day of discharge 150 units of unmodified plus 220 units of protamine zinc insulin was given. The patient had noted at home definite unexplained variations in the insulin requirement from time to time. She had been menstruating regularly about every twenty-eight days; she had noted no relation between the menstrual periods and the insulin requirement.

The body weight without clothing was 116 pounds (52.7 Kg.). Physical examination showed both the liver and the spleen to be palpable. Roentgenograms of the chest and skull showed no significant abnormalities. Those of the joints, especially the joints of the hands and wrists, showed marked loss of cartilage and erosion of the articular spaces, indicating much progression of the arthritic process since November 1935. The basal metabolic rate was —1 per cent, the visual fields were normal, the blood sedimentation rate was normal and the plasma cholesterol value was 116 mg. per hundred cubic centimeters. The erythrocyte count was 4,560,000, the hemoglobin value was 70 per cent (Sahli) and the eosinophils in the blood smear numbered 2 per cent. Marked insensitiveness to insulin was evident when the test devised by Himsworth [28] was carried out.

Drs. Mark H. Rogers, Theodore C. Pratt, Walter Bauer and others cooperated in the treatment of this patient during her long stay in the hospital.

28. Himsworth, H. P.: Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, Lancet **1**:127 (Jan. 18) 1936.

PROTAMINE ZINC INSULIN

CLINICAL OBSERVATIONS AND COMPARATIVE ANALYSIS OF BLOOD SUGAR CURVES OBTAINED WITH USE OF PROTAMINE ZINC INSULIN AND WITH REGULAR INSULIN

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A considerable number of favorable reports on the clinical use of protamine zinc insulin in the treatment of diabetes mellitus have appeared in the literature. The articles of Joslin and his co-workers,[1] Rabinowitch and his co-workers,[2] Wilder[3] and others may be cited as examples. In view of these reports there can be no question regarding the more prolonged action of protamine insulin as compared with that of insulin hydrochloride. It is also obvious that with constant proper laboratory supervision, it is possible to treat patients with diabetes mellitus satisfactorily with the newer forms of insulin and usually with a decrease both in the number of doses and in the quantity of insulin administered. Stress thus far has been on the favorable results and the advantages to be gained from a more uniform regulation of the level of blood sugar. Relatively little has been said of the difficulties encountered in the use of protamine zinc insulin. Certain difficulties nevertheless do occur even after considerable experience has been secured with the use of protamine insulin, sometimes when the patients

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The insulin used in this study was supplied by Eli Lilly & Co., Indianapolis.

Presented before the American College of Physicians, St. Louis, April 23, 1937.

From the Department of Medicine, St. Louis University School of Medicine, and from the Medical Service of the Firmin Desloge Hospital.

1. Joslin, E. P.; Root, H. F.; Marble, A., and White, P.: Protamine Insulin, New England J. Med. **214**:1079-1085 (May 28) 1936. Joslin, E. P.: Diabetes Today and Tomorrow, Ann. Int. Med. **10**:179-193 (Aug.) 1936.

2. (*a*) Rabinowitch, I. M.; Fowler, A. F., and Corcoran, A. C.: Observations on the Action of Protamine and Insulin in the Treatment of Diabetes Mellitus, Canad. M. A. J. **35**:124-129 (Aug.) 1936. (*b*) Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Observations with Protamine Zinc Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, ibid. **35**:239-252 (Sept.) 1936.

3. Wilder, R. M.: The New Insulin, Minnesota Med. **20**:6-15 (Jan.) 1937. Wilder, R. M., and Wilbur, D. L.: Disease of Metabolism and Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **59**:329-364 (Feb.) 1937.

are under care in the hospital but especially when they are not under constant supervision. The use of protamine insulin rather quickly brings to light certain irregularities in its effect on the blood sugar which are likely to be particularly important if the drug is to be introduced in general practice for use by physicians who do not have adequate laboratory control of their patients.

Too much reliance cannot be placed on the urinary sugar value as a measure of the blood sugar value. We have noted frequently that the blood sugar level may be very high and that the urine may contain little or no sugar; and, conversely, sugar has been found to be present in the urine, although the blood sugar level at that time has been within normal limits. This observation is illustrated in many of the cases in the present study and leads one to believe that the renal threshold for sugar may vary in the same individual. The importance of obtaining frequent blood sugar determinations is therefore evident.

In the service for diabetic patients at the Firmin Desloge Hospital my colleagues and I have been quite successful in the use of protamine insulin in many cases. In other cases distinct difficulties have been encountered. We have felt that it would be of value to present frankly the difficulties we have experienced in using protamine insulin. Since one of the main advantages of the new type of insulin has been said to be the fact that fewer injections are required, we have endeavored in as many cases as possible to use one injection per day. Also, rather than complicate the treatment for the patients, we have avoided combining two types of insulin, and in some of the cases in which successful regulation of the carbohydrate metabolism has not been obtained with one dose of protamine insulin, we have tried to obtain it by dividing the dose in two. While it is obvious from the literature that a combination of the two types of insulin often gives good clinical results, it should certainly not be claimed in these instances that the management of the diabetic condition has been simplified by the use of the new preparation. In many cases it actually appears to have rendered treatment more complicated and difficult.

The present report will be confined to a study of 12 patients. Their ages varied from 24 to 70 years. The series included 2 patients who had been in diabetic coma on previous occasions. In all these cases satisfactory results were first obtained with regular insulin hydrochloride, and blood sugar readings were made at 7 and 11 a. m., and at 3 and 7 p. m. The patients were then given protamine zinc insulin. In most cases 75 per cent of the total number of units of regular insulin was given in the form of protamine insulin at 7 a. m. as the initial dose. A period of five to six days was allowed to elapse in order to permit the cumulative effect of protamine zinc insulin to become defi-

nitely established. Then blood sugar readings were again made four times daily at the hours previously designated. If the values showed a satisfactory control of the carbohydrate metabolism during the day, an additional blood sugar reading was made at 3 a. m. to determine whether the metabolism of carbohydrate was satisfactory during the night. Specimens of urine were obtained four times daily, just before the venous puncture for the blood specimen was made. Patients were considered successfully treated with protamine zinc insulin if the blood sugar values with the protamine insulin regimen compared favorably with those obtained during the treatment with regular insulin. For patients unsuccessfully treated with one dose of protamin insulin, two doses were tried.

The effect of varying the time of administration of the protamine insulin was studied as well as the effect of altering the amount of carbohydrate given at each meal. All the patients were hospitalized for the first several weeks of this study. After their discharge from the hospital they returned to the outpatient clinic once a week, where their progress was observed and blood sugar determinations were obtained. Studies of the blood sugar were made with venous blood. The blood proteins were precipitated by the Folin-Wu method, and the blood sugar values were determined for the filtrate by the Shaffer-Somogyi improved copper-iodometric method.[4]

A brief résumé of each case will be presented, together with tables showing the blood sugar levels observed throughout the day, first with the use of regular insulin and then with protamine insulin. A comparison of the respective blood sugar curves can thus be made easily. In these tables the letter R represents regular or old insulin, and the letter P represents protamine insulin. The hours when the samples of blood were obtained and the insulin was administered are indicated in the headings for each table.

REPORT OF CASES

CASE 1.—F. Z. was an electrician aged 47 years, weighing 76 Kg. Diabetes was discovered at the time of his first visit to the diagnostic clinic of the outpatient department, on Oct. 16, 1936. When he was referred to the service for diabetic patients he was given a diet which consisted of 72 Gm. of protein, 100 Gm. of fat and 280 Gm. of carbohydrate. Regulation of the carbohydrate metabolism was successful with this diet when three doses of regular insulin were given, distributed as 33 units in the morning, 17 units at noon and 31 units before the evening meal. The blood sugar curves for two consecutive days showed good control of the carbohydrate metabolism. The patient was then given 45 units of protamine zinc insulin at 7 a. m., and blood sugar readings were made four times daily. After several days, as can be seen from the table, the curves compared favorably with those obtained when the patient was receiving regular insulin. In

4. Shaffer, P. A., and Somogyi, M.: Copper-Iodometric Reagents for Sugar Determination, J. Biol. Chem. **100**:695-713 (May) 1933.

order to determine the efficiency of the metabolism of carbohydrate at night with the protamine insulin regimen, a blood sugar reading was made at 3 a. m. on November 12 and was found to be 35 mg. per hundred cubic centimeters, although the patient at that time experienced no symptoms of hypoglycemia. The adminis-

TABLE 1.—*Data for F. Z. (Case 1)**

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	6 p.m.
11/ 2/36	Blood	154	140	100	125	...	33 R	17 R	31 R
	Urine	0	0	0	0				
11/ 3/36	Blood	162	175	100	125	...	33 R	17 R	31 R
	Urine	0	+	0	0				
11/11/36	Blood	100	176	175	125	60	45 P		
	Urine	0	+	0	0				
11/12/36	Blood	135	195	135	180	35	45 P		
	Urine	0	0	0	0				
11/23/36	Blood	65	155	160	155	80	35 P at 5:30 p.m.		
	Urine	0	0	0	0				
11/24/36	Blood	70	155	150	125	...	35 P at 5:30 p.m.		
	Urine	0	0	0	0				
11/27/36	Blood	60	100	112	170	...	35 P at 7 p.m.		
	Urine	0	0	0	0				
11/28/36	Blood	90	155	135	115	100	35 P at 7 p.m.		
	Urine	0	0	0	0				

* In tables 1 to 12 R indicates regular insulin and P protamine insulin. The values for blood sugar are given in milligrams per hundred cubic centimeters and those for insulin in units.

TABLE 2.—*Data for M. L. (Case 2)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	6 p.m.
12/20/36	Blood	112	80	160	135	...	21 R	.....	20 R
	Urine	+	+	+	+				
12/22/36	Blood	110	100	135	160	...	21 R	.....	20 R
	Urine	+	++	++	++				
1/ 7/37	Blood	60	75	165	185	...	30 P at 10 p.m.		
	Urine	++	+	0	0				
1/ 8/37	Blood	60	35	130	212	...	30 P at 10 p.m.		
	Urine	++	0	0	++				
1/ 9/37	Blood	45	75	120	200	...	30 P at 10 p.m.		
	Urine	+	0	+	+				
1/29/37	Blood	76	100	170	135	75	30 P		
	Urine	0	0	0	0				
1/30/37	Blood	80	155	200	125	...	30 P		
	Urine	+	+	++	+				
2/ 2/37	Blood	80	112	155	135	75	30 P		
	Urine	0	+	+	0				
2/ 3/37	Blood	80	55	195	125	...	30 P		
	Urine	0	0	0	0				
2/18/37	Blood	75	95	150	140	80	30 P		
	Urine	0	0	0	0				

tration of insulin was then advanced to 5:30 p. m. and finally to 7 p. m. Blood sugar readings were made at 3 a. m. on November 23 and again on November 28 and were found to be 80 and 100 mg. per hundred cubic centimeters, respectively. In this case regulation with protamine insulin was considered as successful, requiring only 58 per cent of the former number of units of regular insulin. The number of doses was cut down from three to only one daily.

CASE 2.—M. L., a man aged 66 years, weighing 72 Kg., was found to be suffering from diabetes when examined in the outpatient department and was admitted for regulation of the diet and the dosage of insulin. He was given a diet which consisted of 72 Gm. of protein, 82 Gm. of fat and 220 Gm. of carbohydrate. The urine was free from sugar when insulin hydrochloride was given twice a day (21 units before breakfast and 20 units before supper). Blood sugar readings were made four times daily and were within physiologic limits. The patient was then given 30 units of protamine insulin at 10 p. m. However, the values for sugar at night were high, while those obtained during fasting in the morning were low. The time of administration of the protamine insulin was then changed to 7 a. m., and the blood sugar curves were satisfactory. Blood sugar readings

TABLE 3—*Data for J. B. (Case 3)*

		Time of Examination				Administration of Insulin
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	7 a.m.
7/ 9/36	Blood	125	135	160	165	45 P
	Urine	0	0	0	0	
7/10/36	Blood	125	135	140	170	45 P
	Urine	0	0	0	0	
7/11/36	Blood	150	160	175	175	45 P
	Urine	0	0	0	0	
7/12/36	Blood	135	140	160	125	45 P
	Urine	0	0	0	0	

TABLE 4.—*Data for W. B. (Case 4)*

		Time of Examination				Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	7 a.m.	Noon	6 p.m.
7/ 5/36	Blood	125	160	212	160	22 R	6 R	20 R
	Urine	0	0	0	0			
7/ 6/36	Blood	135	160	120	160	22 R	6 R	20 R
	Urine	0	0	0	0			
7/13/36	Blood	80	135	160	135	40 P		
	Urine	0	0	0	0			
7/14/36	Blood	112	185	160	135	40 P		
	Urine	0	0	0	0			
7/15/36	Blood	112	160	180	135	40 P		
	Urine	0	0	0	0			

were made at 3 a. m. for several successive nights and were always within normal limits. The patient was discharged when taking 30 units of protamine insulin once daily. Blood sugar readings were made on several occasions in the outpatient clinic and were always within normal limits. In this case, therefore, satisfactory regulation was secured with one dose of protamine insulin which was 75 per cent of the previous dose of regular insulin.

CASE 3.—J. B., a man aged 55 years, weighing 75 Kg., was known to have had diabetes for three years. With a diet of 75 Gm. of protein, 135 Gm. of fat and 160 Gm. of carbohydrate he required three doses of regular insulin for satisfactory regulation (23 units in the morning, 6 units at noon and 23 units at night). Regulation was finally secured with 45 units of protamine insulin at 7 a. m. Therefore satisfactory regulation was obtained with a single dose of protamine insulin, 72 per cent of the former dose of regular insulin being all that was required.

CASE 4.—W. B., a man aged 59 years, weighing 70 Kg., was given a diet consisting of 70 Gm. of protein, 100 Gm. of fat and 200 Gm. of carbohydrate. Satisfactory regulation was obtained with three doses of old insulin (22 units in the morning, 6 units at noon and 20 units before the evening meal). Equally successful regulation was obtained with 40 units of protamine insulin given at 7 a. m. in one dose which constituted 83 per cent of the former dose of regular insulin.

CASE 5.—M. F. was a woman aged 62 years, weighing 64 Kg. With a diet consisting of 64 Gm. of protein, 98 Gm. of fat and 196 Gm. of carbohydrate, satisfactory regulation was obtained with 3 doses of old insulin (30 units in the

TABLE 5.—*Data for M. F. (Case 5)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	6 p.m.
9/22/36	Blood	155	125	80	112	..	30 R	16 R	24 R
	Urine	0	0	0	0				
9/23/36	Blood	160	100	110	210	..	30 R	16 R	24 R
	Urine	0	0	0	0				
9/30/36	Blood	80	75	175	225	94	45 P		
	Urine	0	0	0	0				
10/ 3/36	Blood	100	110	120	100	..	45 P		
	Urine	0	0	0	0				
10/ 4/36	Blood	100	112	175	245	..	45 P		
	Urine	0	0	0	0				

TABLE 6.—*Data for G. M. (Case 6)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	3 p.m.
2/10/37	Blood	160	90	135	185	...	28 R	10 R	20 R
	Urine	+	0	0	++				
2/15/37	Blood	75	135	200	150	48	40 P at 9 p.m.		
	Urine	+	++	+++	+				
2/16/37	Blood	55	75	135	150	...	40 P at 9 p.m.		
	Urine	+	+	+	+				
3/ 2/37	Blood	120	235	135	160	112	35 P		
	Urine	0	+	0	0				
3/ 3/37	Blood	112	200	135	125	100	35 P		
	Urine	0	++	++	0				

morning, 16 units at noon and 24 units in the evening). Fairly good regulation was obtained with 45 units of protamine insulin given in one dose at 7 a. m. The blood sugar level at 7 p. m., although a little higher than desirable, could easily have been lowered by giving a small dose of old insulin with the evening meal. This elevated level did not persist for any great length of time, since the 3 a. m. reading was 94 mg. per hundred cubic centimeters.

In this case successful regulation was obtained with one dose of protamine insulin, whereas three doses of old insulin were previously necessary. This patient required only 77 per cent of the previous dose of old insulin given as protamine insulin, a saving of 23 per cent.

Case 6.—G. M., aged 63 years, weighing 68 Kg., was known to have had diabetes for five years. With a diet containing 72 Gm. of protein, 70 Gm. of fat and 300 Gm. of carbohydrate, satisfactory regulation was secured with three

doses of old insulin (28 units in the morning, 10 units at noon and 20 units in the evening). Protamine insulin was given in a single dose at 9 p. m. Blood sugar readings made four times daily showed fairly good control with one dose. However, when the blood sugar reading was made at 3 a. m., it was found to be 48 mg. per hundred cubic centimeters, although the patient at that time showed no evidence of hypoglycemia. The dose of insulin was lowered to 35 units and was given at 7 a. m. This produced a satisfactory regulation, and the blood sugar reading at 3 a. m. was not unusually low.

Regulation of the diabetic condition was successful, the number of doses was reduced from three to one and the dose of insulin was reduced by 40 per cent.

The cases so far presented may be taken as typical examples of successful treatment. In these cases definite advantages can be demonstrated in the use of protamine zinc insulin. In the following cases, distinctly more difficult problems were presented:

CASE 7.—For C. W., aged 66 years, weighing 62 Kg., the diagnosis of diabetes mellitus was made two weeks before her admission to the hospital. She was given

TABLE 7.— *Data for G. W. (Case 7)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	3 p.m.
12/14/36	Blood	85	80	160	160	..	20 R	.....	16 R
	Urine	0	0	0	0				
12/15/36	Blood	85	90	100	170	..	20 R	.....	16 R
	Urine	+	+	0	0				
1/ 9/37	Blood	90	185	270	260	..	25 P at 10 p.m.		
	Urine	++	+++	+++	+++				
2/ 1/37	Blood	112	160	212	200	50	30 P		
	Urine	++	+++	+++	++				
2/ 2/37	Blood	85	160	200	235	..	30 P		
	Urine	+++	++	++	++				

a diet consisting of 62 Gm. of protein, 80 Gm. of fat and 220 Gm. of carbohydrate. Regulation was obtained with two doses of regular insulin (20 units in the morning and 16 units in the evening).

After satisfactory regulation was obtained, protamine zinc insulin was given at 10 p. m. in a single dose of 25 units. In the afternoon and evening the blood sugar levels were very high. The dose of protamine insulin was raised to 30 units and was given at 7 a. m. Better blood sugar values were obtained during the day; however, at 3 a. m. the patient experienced a hypoglycemic reaction, and the blood sugar readings made the following day showed an unsatisfactory regulation of the carbohydrate metabolism; the urine showed 2 plus and 3 plus sugar.

Successful regulation was not obtained with one dose of protamine zinc insulin. We did not give this patient both types of insulin, since satisfactory regulation was obtained with two doses of old insulin and we considered it inadvisable to complicate the treatment of diabetes in this case by using two types of insulin.

CASE 8.—D. W., a man aged 31 years, weighing 72 Kg., was known to have had diabetes for two years. He was given a diet which consisted of 72 Gm. of protein, 100 Gm. of fat and 200 Gm. of carbohydrate, with three doses of regular insulin (28 units at 7 a. m., 12 units at noon and 26 units at 5 p. m.). Fairly good regulation was obtained; although in the morning during fasting the blood

sugar content was always high, the blood sugar values throughout the day were within normal limits. This patient was given 45 units of protamine insulin at 7 a. m.; as can be seen from the accompanying table, not only were the blood sugar peaks high, but the type of curve varied from day to day. Further evidence of the unsatisfactory regulation and lack of uniform action of protamine insulin in this case was the hypoglycemic reaction which occurred at 3 a. m. on Oct. 4, 1936. The blood sugar value at that time was 44 mg. per hundred cubic centimeters.

In this case satisfactory regulation was not obtained with one dose of protamine insulin.

TABLE 8.—*Data for D. W. (Case 8)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	3 p.m.
9/29/36	Blood	250	160	135	115	...	28 R	12 R	26 R
	Urine	+++	+++	0	0				
9/30/36	Blood	255	120	90	80	...	28 R	12 R	26 R
	Urine	0	+	0	0				
10/ 3/36	Blood	75	90	125	235	...	45 P		
	Urine	++	++	0	++				
10/ 4/36	Blood	80	275	200	250	44	45 P		
	Urine	+	+++	+++	+++				
10/14/36	Blood	60	160	225	260	...	40 P		
	Urine	0	+	++	++				

TABLE 9.—*Data for E. W. (Case 9)*

		Time of Examination					Administration of Insulin			
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 p.m.	7 a.m.	Noon	6 p.m.	10 p.m.
9/11/36	Blood	200	145	155	135	...	25 R	10 R	10 R	10 R
	Urine	+	+++	++	++					
9/12/36	Blood	235	105	85	190	...	25 R	10 R	10 R	10 R
	Urine	+	+	0	+					
10/ 9/36	Blood	60	220	180	190	35	30 P			
	Urine	0	+	0	0					
10/12/36	Blood	100	135	125	212	30	25 P			
	Urine	0	0	0	0					
10/14/36	Blood	155	250	190	178	44 at 9 p.m.	25 P			
	Urine	0	+++	+++	++					

CASE 9.—E. W., a man aged 24 years, weighing 76 Kg., was known to have had diabetes for two years. He was given a diet of 80 Gm. of protein, 185 Gm. of fat and 260 Gm. of carbohydrate. Satisfactory regulation could not be obtained with less than four doses of regular insulin because of a labile type of blood sugar curve. The fourth dose was given at 10 p. m. with 200 cc. of orange juice. Any attempt to lower the blood sugar level during fasting by raising the 10 p. m. dose of insulin caused a hypoglycemic reaction between the hours of 1 and 3 a. m. However, with protamine zinc insulin the results were no better; the number of hypoglycemic reactions were more frequent with the new than with the old type of insulin. On one day it is seen that the blood sugar level fell from 212 mg. to 30 mg. per hundred cubic centimeters during a period of eight hours and from 178 to 44 mg. per hundred cubic centimeters within two hours while the patient was receiving protamine insulin.

In this case the use of protamine insulin was not continued.

CASE 10.—M. H., a woman aged 70 years, weighing 70 Kg., was known to have had diabetes for fifteen years. She was given a diet containing 70 Gm. of protein, 90 Gm. of fat and 200 Gm. of carbohydrate. Satisfactory regulation was obtained with three doses of old insulin (25 units in the morning, 8 units at noon and 10 units in the evening). She was then given 30 units of protamine insulin in one dose at 10 p. m. A hypoglycemic reaction occurred at 3 a. m. Giving the insulin at 7 a. m. eliminated the hypoglycemic reaction. However, the blood sugar curves

TABLE 10.—*Data for M. H. (Case 10)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	6 p.m.
12/27/36	Blood	85	115	100	160	...	25 R	8 R	10 R
	Urine	+	+	+	+				
12/28/36	Blood	85	112	90	150	...	25 R	8 R	10 R
	Urine	+	+	++	+				
1/ 8/37	Blood	90	235	212	225	35	30 P at 10 p.m.		
	Urine	+	+++	+++	+++				
2/ 4/37	Blood	125	200	230	235	112	35 P		
	Urine	0	++	+++	+++				
2/ 8/37	Blood	100	175	250	175	...	35 P		
	Urine	0	++	+++	++				

TABLE 11.—*Data for R. J. (Case 11)*

		Time of Examination				Administration of Insulin				
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	7 a.m.	Noon	6 p.m.	7 p.m.	10 p.m.
8/21/36	Blood	185	80	105	150	30 R	12 R	16 R	.....	12 R
	Urine	0	0	0	0					
8/22/36	Blood	150	80	100	160	30 R	12 R	16 R	.....	12 R
	Urine	0	0	0	0					
8/27/36	Blood	285	315	235	180	45 P				
	Urine	0	0	0	0					
9/ 7/36	Blood	300	375	250	225	35 P	15 P			
	Urine	+	++++	++	+					
9/16/36	Blood	75	210	260	230	35 P	.....	.....	15 P	
	Urine	+	+	++++	+++					
9/28/36	Blood	60	150	275	275	40 P	.....	.....	15 P	
	Urine	0	+	+	++					
9/29/36	Blood	70	40	80	100	40 P	.....	.....	15 P	
	Urine	++	0	0	0					
9/30/36	Blood	50	275	250	185	40 P	.....	.....	10 P	
	Urine	0	++	+++	+++					
10/ 1/36	Blood	150	100	120	90	40 P	.....	.....	10 P	
	Urine	0	0	0	0					

were much inferior to those obtained when three doses of regular insulin were being given.

In this case, regulation was not as satisfactory with protamine insulin as with insulin hydrochloride.

CASE 11.—R. J., a man aged 51 years, weighing 79 Kg., was known to have had diabetes for six years. Diabetic coma occurred in 1935. This patient was given a diet consisting of 79 Gm. of protein, 116 Gm. of fat and 190 Gm. of carbohydrate. Regulation was difficult with insulin hydrochloride but was finally obtained with four doses. The fourth dose was given at 10 p. m. with 200 cc. of orange juice. Treatment was then started with 45 units of protamine insulin given in a single dose at 7 a. m. This was unsatisfactory. The effect of splitting the dose of

protamine insulin in two was next tried. Thirty-five units was given at 7 a. m. and fifteen units at noon. This did not improve the blood sugar curve, and the time for the second dose was changed to 7 p. m., with still less satisfactory results. As can be readily seen from the accompanying table, the blood sugar curves varied greatly from day to day.

In this case, satisfactory regulation was not obtained with one or two doses of protamine insulin.

Case 12.—M. S., a woman aged 66 years, weighing 62 Kg., was known to have had diabetes for six years and had experienced diabetic coma on three separate occasions. She received a diet which consisted of 62 Gm. of protein, 90 Gm. of fat and 190 Gm. of carbohydrate. Regular insulin was given three times daily (32 units before breakfast, 10 units before the noon meal, 34 units before the evening meal). The blood sugar value in the morning during fasting was very

Table 12.—*Data for M. S. (Case 12)*

		Time of Examination					Administration of Insulin		
Date	Sugar	7 a.m.	11 a.m.	3 p.m.	7 p.m.	3 a.m.	7 a.m.	Noon	6 p.m.
7/19/36	Blood	300	200	100	125	..	32 R	10 R	34 R
	Urine	0	++	0	0				
7/20/36	Blood	325	125	75	135	..	32 R	10 R	34 R
	Urine	0	++	0	0				
7/24/36	Blood	200	275	285	235	40	55 P		
	Urine	0	+++	++	0				
7/25/36	Blood	235	135	35	115	..	35 P		
	Urine	0	++++	0	0				
8/18/36	Blood	75	250	350	235	..	35 P	.....	15 P
	Urine	0	+	++++	+++				
8/24/36	Blood	150	200	190	125	..	33 P	.....	15 P
	Urine	0	+	++	0				
8/25/36	Blood	125	225	225	175	..	33 P	.....	15 P
	Urine	0	+++	++	0				
8/27/36	Blood	112	135	230	235	..	35 P	15 P	
	Urine	++	0	+	+				
9/28/36	Blood	50	160	160	165	..	35 P	15 P	
	Urine	0	0	0	+				
9/29/36	Blood	35	125	185	270	..	35 P	15 P	
	Urine	0	0	0	++				

high, but the values during the day were within normal limits. She was given 55 units of protamine insulin at 7 a. m. On the fourth day of this regimen, she had a severe hypoglycemic reaction at 5 a. m. The blood sugar content was 40 mg. per hundred cubic centimeters at that time. The dose of protamine insulin was then divided in two; 35 units was given at 7 a. m. and 15 units at 7 p. m. When this was found to be unsatisfactory, the effect of giving the second dose before the noon meal instead of at 7 p. m. was tried. The blood sugar curves were found to be satisfactory, and the patient was discharged, receiving 35 units of protamine insulin at 7 a. m. and 15 units at noon. She returned two weeks later in a state of severe hypoglycemic shock. This condition was relieved by the administration of dextrose intravenously. Thinking that the hypoglycemic reaction had been due to improper dietary regulation on the part of the patient, we continued to give her protamine insulin as on the day of her previous discharge. The blood sugar value during fasting on two consecutive mornings was found to be dangerously low, so that the use of two doses of protamine insulin had to be discontinued.

In this case regulation was not satisfactory with one or two doses of protamine zinc insulin.

COMMENT

Of the present series of 12 patients with diabetes mellitus chosen at random, 6, who had previously required two or three doses of regular insulin, showed satisfactory regulation with one dose of protamine zinc insulin. Consequently, a saving of from 17 to 42 per cent was noted when protamine zinc insulin was substituted for the regular insulin hydrochloride in these cases. Five of these patients did well when the protamine insulin was given at 7 a. m., while in one case regulation was obtained only by the administration of protamine insulin at 7 p. m. (table 1). In the great majority of cases the lowest blood sugar level for the twenty-four hour period was found to occur twenty hours after the injection when the protamine insulin was given at 7 a. m. and five hours later when it was given at 10 p. m. The only exception to this rule was noted in case 1; the low point was observed after twelve hours when the protamine insulin was given at 7 p. m. (table 1). It was our constant observation that if protamine insulin given in a single dose was unsuccessful in producing satisfactory blood sugar curves, splitting the dose in two frequently caused even greater variations in the blood sugar curves than did one dose (tables 11 and 12).

When the action of regular insulin is studied it is always observed that a given amount of insulin will cause a fairly constant drop in the blood sugar level provided the diet remains unchanged and no infectious process is present; so that if the blood sugar reading is taken at the same time on several consecutive days, it will not vary to any great extent from the reading taken at the same time the day previously. Also the type of curve obtained when two or three doses of regular insulin are given will not vary to any great extent from day to day even in cases of more severe diabetes. This observation also holds true for the patients successfully regulated with protamine insulin. However, the patients who were unsuccessfully treated with one or two doses of protamine insulin showed blood sugar curves which varied greatly from day to day (tables 8, 9, 11 and 12). This observation suggests that the action of protamine insulin in these cases is not uniform. This may be due to a difference in the rate of absorption or to factors associated with the reactivation of the protamine insulin. For example, in table 9 it is seen that on the third day there occurred a fall in blood sugar content from 178 to 44 mg. per hundred cubic centimeters within a period of two hours.

The inability of protamine insulin to prevent abnormally high elevations of the blood sugar level after meals is clearly demonstrated in all the cases in which treatment was unsuccessful and to a lesser degree in 2 of the cases in which treatment was successful (tables 5 to 12). The blood sugar content in these cases will be noted to be much higher,

more frequently in the absorptive state with protamine than with the regular insulin. This is to be expected, because with protamine insulin the rate of absorption from the subcutaneous tissue is gradual and therefore there is only a small amount of insulin available for immediate use at any given time to cope with a sudden increase of sugar in the blood, such as occurs after meals, and for that reason a higher blood sugar content will be noted during the hours following meals when protamine is used. In this respect a rapidly acting insulin given before meals is more physiologic in its action than a slowly acting insulin.

In further support of the conclusion that protamine is absorbed slowly and that the fall in blood sugar content is gradual is the observation reported by various investigators [2a] that many patients may show hypoglycemia without experiencing the symptoms which are associated with it. We have corroborated this observation many times, particularly when we have had occasion to make the blood sugar reading at 3 a. m. At that time the blood sugar level is frequently found to be below 50 mg. per hundred cubic centimeters, but the patient does not have symptoms of hypoglycemia. This occurrence of "symptomless hypoglycemia" with slowly acting insulin we consider a great disadvantage which may prove to be quite harmful. It is well known that an anginal attack may be brought on by a low blood sugar content, particularly in diabetic patients with arteriosclerosis.[5] Wilder [6] has recently reported that if in dogs the blood sugar content is kept at a low level for a certain length of time, the attempt to raise the content by the intravenous administration of dextrose frequently results in death of the animal. Somogyi [7] has presented evidence to show that after hypoglycemia there occurs a compensatory period of hyperglycemia in the diabetic patient, with an increased degree of glycosuria as well as a reduced tolerance for sugar. We therefore believe that it is better for a patient to have a moderately elevated blood sugar level during the night than a low one. Since with the use of protamine insulin the low point usually falls around 3 a. m. and hypoglycemia may occur without symptoms, the importance of determining the blood sugar level at this hour is at once evident. When employing protamine insulin we found that the principles commonly followed for treatment with regular insulin had to be modified. Whereas with regular insulin the highest blood sugar value obtained during the twenty-four hour period is taken

5. Parsonnet, A. E., and Hyman, A. S.: Insulin Angina, Ann. Int. Med. **4**: 1247-1256 (April) 1931.

6. Wilder, R. M.: Clinical Investigations of Insulins with Prolonged Activity, Ann Int. Med. **11**:13-30 (July) 1937.

7. Somogyi, M.: Hyperglycemic Response to Hypoglycemia in Diabetic and in Healthy Individuals, Proc. Soc. Exper. Biol. & Med. **38**:51-55 (Feb.) 1938.

as the important figure and for that reason the morning value during fasting is the chief criterion of the state of regulation of the diabetes, when protamine insulin is used the low point also has to be watched. For that reason a 3 a. m. estimation of the blood sugar content is to be recommended. This, of course, is difficult to secure unless the patient is in a hospital.

Examination of the charts, as already pointed out, reveals the fact that if protamine zinc insulin is administered at 7 a. m., the lowest blood sugar value in the twenty-four hour period will be obtained in nearly all cases after twenty hours. On the other hand, if the injection of insulin is made at 10 p. m., the low point will in most cases occur after five hours. This fact makes the administration of protamine insulin at night unsuitable in most cases, since the greatest effect of protamine insulin would be desirable after the elapse of about ten hours, when breakfast is due (this occurred in only 1 of our series of cases; table 1). Why the low point should occur after five hours when protamine insulin is given at 10 p. m. is a matter of speculation. One would expect that since the effect of protamine insulin is continuous, the fall in blood sugar level ought to continue well after 3 a. m., so that the 7 a. m. value would be lower than the 3 a. m. value. However, as can be seen from tables 2, 5 and 6, such is not the case. After this low point, if a hypoglycemic reaction does not occur the blood sugar level will rise, so that the 7 a. m. value will be higher than the 3 a. m. value. A possible explanation is that the falling blood sugar level causes stimulation of the adrenal glands, with consequent liberation of glycogen from the liver so that the blood sugar value will rise once this critical level is reached. When this compensation does not take place, a hypoglycemic reaction will occur.

SUMMARY

Fluctuations in the blood sugar values for 12 diabetic patients who were first treated with regular insulin and then with protamine zinc insulin are presented.

In 50 per cent of our cases, regulation was successful with one daily injection of protamine insulin, and the total requirement for insulin was reduced from 42 to 17 per cent.

In 50 per cent of the cases, satisfactory regulation could not be obtained with either one or two doses of protamine insulin.

In agreement with the reports of other investigators we found that protamine insulin had a more gradual and prolonged lowering effect on the blood sugar content than did regular insulin hydrochloride.

In 5 of our cases in which treatment with protamine insulin was successful, the insulin was administered at 7 a. m. In 1 case regulation was obtained when the protamine insulin was given at 7 p. m.

The importance of determining the blood sugar value at 3 a. m. when regulation has apparently been obtained with protamine insulin is pointed out.

The renal threshold for dextrose may vary for an individual from time to time.

CONCLUSION

In our series of cases the lowest blood sugar level during the twenty-four hour period was found to occur (*a*) after twenty hours when the protamine insulin was injected at 7 a. m. and (*b*) after five hours and in 1 case after twelve hours when it was injected at 10 p. m.

In view of the uncertainty regarding the occurrence of the lowest blood sugar level after the injection of protamine insulin, it is obvious that the use of this material by physicians for the treatment of patients in their homes is likely to be associated with more frequent low blood sugar levels than when regular insulin hydrochloride is used.

Since many believe that hypoglycemia is more dangerous to the patient's well-being and therefore more to be avoided than moderate hyperglycemia, a distinct question is raised regarding the selection of patients amenable to treatment with protamine insulin.

DIFFUSE ARTERIAL DISEASE WITH HYPERTENSION

TWO UNUSUAL CASES OF CONTRASTING TYPES

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For the last fifteen years a group at the Mayo Clinic have been interested in the difficult problem of diffuse arterial disease with hypertension. Periodically an unusual case of this disease is encountered which upsets prevailing ideas and compels an alteration of views with regard to the general problem. In this paper we wish to describe and discuss 2 such cases. They are undoubtedly extreme examples, but they present interesting features that are not altogether typical and accentuate important points which may add to the knowledge of the group of more general examples. The patients were both physicians in the prime of life, and diffuse arterial disease was the cause of death in both cases. The clinical course and the retinal and pathologic data will be stressed in this report.

CASE 1.—On May 15, 1936, the first patient, a physician 46 years of age, came to the clinic complaining of profound fatigue, pains in the extremities, irregularity of the heart beat, polyuria and nocturia. The family history was irrelevant. He had diphtheria at the age of 6 years and mumps at 13, followed by orchitis on the right side. He had gonorrheal urethritis at 19. His tonsils were removed when he was 24, and he underwent appendectomy when he was 31.

He attributed his current illness to an incident which occurred in February, three months before his visit to the clinic. When returning from a midnight visit to a patient, he suffered severe exposure when his car stalled and he had to crawl under it to make some repairs, the temperature being 24 F. below zero. Four days later chilly sensations, fever and backache in the lumbar region developed. Fever continued daily, the temperature mounting to 103 or 104 F. daily for two weeks. Later he became progressively more fatigued. In March nocturia appeared, and often he passed 1,500 to 2,000 cc. of urine during the night. In April he noticed that his heart beat was irregular. He continued to practice medicine, however, in spite of these symptoms.

On examination at the clinic on May 15 his blood pressure in millimeters of mercury was 165 systolic and 120 diastolic (fig. 1). He weighed 195 pounds

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(88.6 Kg.). Vision in the right eye was 6/7; in the left, 6/6. The ocular fundi were normal. There were occasional extrasystoles, but no other cardiac abnormality was detected. A single specimen of urine contained no albumin or casts, and only

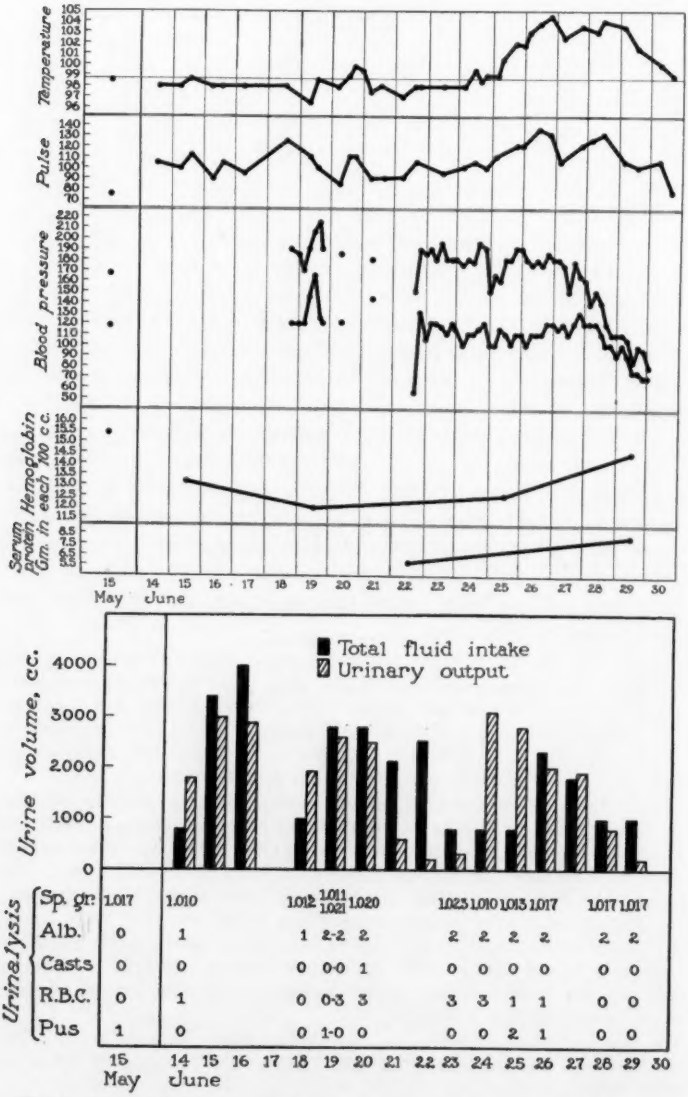
Temperature
Pulse
Blood pressure
Serum Hemoglobin Gm. in each 100 c.c.
Serum protein Gm. in each 100 c.c.
15 May
14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 June
Urine volume, c.c.
Total fluid intake
Urinary output
Urinalysis
Sp. gr. 1.017 1.010 1.012 1.011 1.021 1.020 1.023 1.010 1.013 1.017 1.017 1.017
Alb. 0 1 1 2-2 2 2 2 2 2 2 2
Casts 0 0 0 0-0 1 0 0 0 0 0 0
R.B.C. 0 1 0 0-3 3 3 3 1 1 0 0
Pus 1 0 0 1-0 0 0 0 2 1 0 0

Fig. 1 (case 1).—Charts showing the variation in temperature, pulse rate and blood pressure, in the concentrations of hemoglobin and protein in the blood and serum, in intake of fluid and volume of urine and in results of urinalyses.

6 pus cells were present per high power field. The blood urea content was 26 mg. per hundred cubic centimeters (table 1). Roentgenograms of the thorax and of the region of the kidneys, ureters and bladder were normal. No definite diagnosis was established, and the patient was sent home to rest.

One week after the patient left the clinic he began to vomit whenever he ate, and often he strained and tried to vomit even when his stomach was empty. He had severe headaches once or twice weekly and said he felt as though his

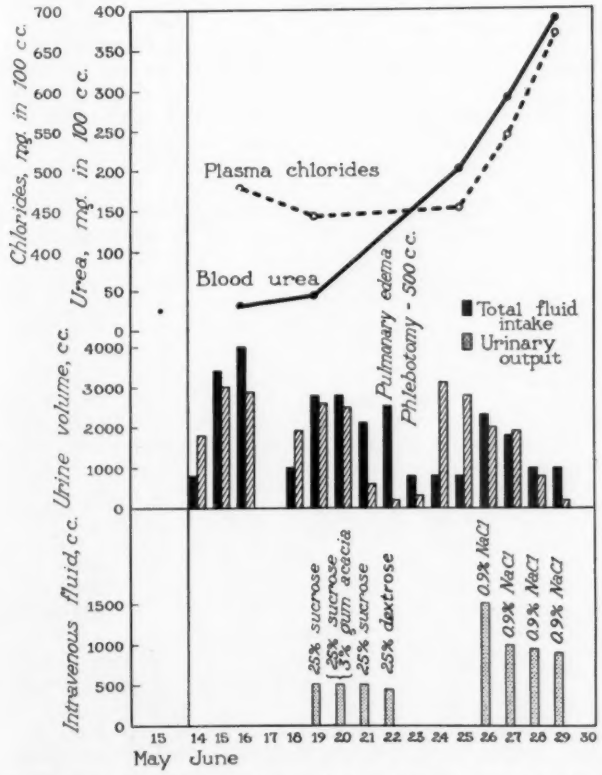

Fig. 2 (case 1).—Chart showing variations in blood urea and plasma chloride values in relation to intake of fluid and volume of urine.

head were in a vise. He would sometimes drop off to sleep while consulting with a patient. He had spells of severe crying. Pains in the extremities became marked and "drove him wild." One week before his second visit he awakened to find that his vision was dim, and subsequently he was able to read only with great difficulty.

He returned to the clinic on June 14, 1936. While making a reexamination, Dr. F. A. Willius noted that the patient's heart was overactive. The heart rate

TABLE 1.—*Data on the Blood (Case 1)*

	First Visit		Second Visit							
Date, 1936	5/15	5/16	6/15	6/16	6/19	6/22	6/25	6/26	6/27	6/29
Hemoglobin, Gm. per 100 cc.	15.4	...	13.3	...	11.9	...	12.5	...	...	14.5
Erythrocytes, millions per cu. mm.	4.05	...	3.59	...	4.09	...	3.37	...	...	...
Leukocytes, per cu. mm.	8,900	...	15,200	...	11,000	...	22,000	25,100	...	...
Lymphocytes, per cent	9	...	10.5	...	8.5	...	....	8	...	...
Monocytes, per cent.	7.5	...	7.5	...	5	...	....	4.5	...	...
Neutrophils, per cent.	80.5	...	80	...	86	...	....	86.5	...	...
Eosinophils, per cent.	2.5	...	1.5	...	0.5	...	....	...	...	...
Basophils, per cent.	0.5	...	0.5	...	....	...	....	...	...	...
Myelocytes, per cent.	....	...	....	...	....	...	....	1	...	...
Normoblasts, per cent.	....	...	....	...	....	...	....	1.5	...	...
Morphologic appearance of blood smear	No features of pernicious anemia		....	...	....	Toxic, 2*	....	Toxic, 3*	...	...
Urea, mg. per 100 cc.	....	26	....	32	44	...	202	...	291	390
Creatinine, mg. per 100 cc.	....	...	....	...	....	...	8.8	...	8.4	8.8
Serum sulfate, mg. per 100 cc.	....	...	....	...	4.2	...	....	...	...	...
Sugar, mg. per 100 cc.	....	109	....	102	....	...	....	...	...	...
Plasma chloride (as sodium choride), mg. per 100 cc.	....	...	....	481	445	...	455	...	554	669
Carbon dioxide-combining power of plasma, volumes per cent.	....	...	....	...	70	...	53	...	57	56
Urea clearance, cc. per minute.	....	...	....	...	58	...	....	...	...	...
Volume of urine, cc. per hour.	....	...	....	...	255	...	....	...	...	...
Sulfate clearance, cc. per minute.	....	...	....	...	55	...	....	...	...	...
Plasma cholesterol, mg. per 100 cc.	....	...	....	...	....	151	....	...	...	...
Serum calcium, mg. per 100 cc.	....	...	....	...	....	8	....	...	...	...
Serum protein, Gm. per 100 cc.	....	...	....	...	....	5.6	....	...	...	8.2
Albumin-globulin ratio	....	...	....	...	....	1:1.2	....	...	...	...
Serum nonprotein nitrogen, mg. per 100 cc.	....	...	....	...	....	67	....	...	...	...
Serum sodium, mg. per 100 cc.	....	...	....	...	....	313	313	...	...	414
Serum potassium, mg. per 100 cc.	....	...	....	...	....	12.8	17.6	...	...	17.9
Hematocrit reading, %	....	...	....	...	....	...	36	...	...	...

* Grade.

was 108 per minute, and the tones were tumultuous. There was marked accentuation of the aortic second sound without apparent enlargement of the heart. Dr. Willius suggested that a vasospastic type of hypertension might be developing. A roentgenogram of the stomach was made to rule out any local lesion as a possible explanation for the vomiting; it revealed no abnormality. Routine urinalysis showed the presence of a trace of protein and a few erythrocytes.

The patient was admitted to the hospital on June 18. At that time there was no dyspnea, and only slight cyanosis was noted. He looked pale. There was slight puffiness of the eyelids, which he believed was natural to him. His vision was 6/15 in the right eye and 6/10 in the left. He was able to read Jaeger test type 0.50 with glasses. The visual fields were roughly normal. The pupils reacted to light and in accommodation. Ophthalmoscopic examination revealed localized and generalized narrowing of the retinal arterioles (graded 1 to 2 in the larger and 3 in the smaller ones) without visible evidences of sclerosis, edema of the optic disks, diffuse edema of the peripapillary retina, scattered cotton-wool patches and hemorrhages, a few yellow foci in the choroid and, in the right eye, extensive subretinal edema which had produced detachment of the lower part of the retina. This picture resembled that seen at times in eclamptic toxemia of pregnancy and was interpreted as indicating acute angiospastic retinitis.[1] It was thought at this time that the yellow foci in the choroid might represent localized spasms in the choroid arteries, but in view of the histologic observations they were probably due to hyaline infiltration in the walls of the arteries of the choroid. The patient's breath was not uremic, and his lungs were clear. There was a systolic heave over the entire precordium, and the left nipple rose and fell with each heart beat. The cardiac borders extended 3 cm. to the right and 11 cm. to the left of the midsternal line. The cardiac action was regular. There was a short aortic systolic murmur, followed by an accentuated second sound (accentuation, grade 2 plus). The abdomen was soft on palpation. The liver could not be felt. The peripheral sclerosis was graded 3 and was of the rubbery type. The patient had no edema. There was no gross neurologic abnormality; Kernig's sign and rigidity of the neck were absent. There was, however, marked generalized muscular tenderness, particularly in the biceps brachii and in the supraspinatus and quadriceps extensor groups.

On June 20, two days later, urinalysis revealed the presence of albumin, grade 2; erythrocytes, grade 3, and a few hyaline casts (fig. 1). The arterioles of the retina showed increased generalized and localized spasm. The edema had receded to some extent from the upper portion of the retina, but more cotton-wool patches were present, and the lower part of the retina in each eye was definitely detached as a result of the subretinal edema. Culture of the blood made on June 21 was sterile. On that same day examination of the capillaries of the nailfold by the technic of Lombard revealed fairly long loops in which both limbs were decreased in caliber; the flow was markedly increased and of the spurting type, but the number of loops in each area was about normal.

On June 22 the patient was not clear mentally, and the urinary output for the preceding twenty-four hours was only 600 cc. (figs. 1 and 2). It was discovered that the liver had descended to 9 cm. below the right costal margin in the mid-clavicular line. At 1:30 p. m. on the same day an intravenous infusion of 25 per cent solution of dextrose was being given; 450 cc. had run into the vein when

1. Wagener, H. P.; Barker, N. W., and Burke, C. F.: Acute Angiospastic Retinitis: Occurrence in Cases of Severe Hypertension and Renal Disease, Am. J. M. Sc. **185**:517-529 (April) 1933.

the patient suddenly became cyanosed and had to sit up in bed for breath. He coughed up frothy blood-stained sputum. Bubbling rales were heard over the entire pulmonary field.

On June 23 at 8 a. m. the patient seemed more irritable than usual. His respirations were periodic, but no actual apneic periods were noted. The pulse rate varied from moment to moment in a remarkable manner, slowing to 64 beats and then, within a few seconds, increasing to 104 beats per minute. These variations had no exact relation to respiratory changes. The total urinary output had dropped in the previous twenty-four hours to only 180 cc. (fig. 1). On percussion the area of cardiac dulness was found to be definitely widened, measuring 3.5 cm. to the right and 13 cm. to the left of the midsternal line. No rales or other abnormal signs could be discovered on examination of the thorax, although a roentgenogram showed diffuse opaque patches throughout both lungs (fig. 3). The cerebrospinal fluid obtained at 11 a. m. was clear, the initial subarachnoid pressure was 30 cm. of water and the response to the Queckenstedt test was prompt and satisfactory. At 3:30 p. m. phlebotomy was performed, and 500 cc. of blood was removed.

On June 24 at 8 a. m. the patient seemed slightly drowsy but answered questions intelligently. There was some twitching of the arms. The neck was not stiff, and Kernig's sign was not present. On this day reexamination of the capillaries of the nailfold showed an increased number of loops in each field; otherwise there was no change, and the capillary blood was not cyanotic.

On June 25 the patient's temperature rose to 102 F. (fig. 1). The electrocardiographic tracings made on June 19 and 23 showed no characteristic or distinct abnormalities. A culture was made of a specimen of urine obtained by catheter on that day and was found to be sterile.

On June 26 at 8 a. m. the patient was in a peculiar restless semicomatose state. He was able to obey simple commands. There was no other gross neurologic abnormality. His respirations continued to be periodic, and, in addition, there were apneic periods lasting as long as ten seconds. Chemical analysis of the blood revealed marked renal insufficiency (table 1 and fig. 2).

On June 27 at 8 a. m. the cerebrospinal fluid was clear, and the initial subarachnoid pressure was 2 cm. of water. The apneic periods were as long as fifteen seconds. No evidence of meningeal irritation was present, and no organisms were seen in the stained smears of cerebrospinal fluid. Ophthalmoscopic examination revealed an increase in the edema of the retina. The detached portions of the retina were elevated about 8 diopters. The disks were definitely edematous, the elevation measuring 2 diopters. Cotton-wool patches and hemorrhagic areas were quite numerous. Punctate areas of exudate in the macular region of the edematous retina indicated the commencing formation of star figures. A roentgenogram of the thorax revealed clear pulmonary fields (fig. 3).

On June 28 at 8 a. m. the patient was throwing his arms and legs around in bed. There was no cyanosis. The pupils were dilated. Examination of the blood indicated further impairment of renal function (table 1 and fig. 2).

On June 29 the heart had decreased in size. On percussion its borders were found to extend 3 cm. to the right and 10.5 cm. to the left of the midsternal line. The heart sounds were barely audible, and there was a to and fro leathery murmur in the third interspace to the left of the sternum. The cardiovascular findings were those of shock. Culture of the blood made on this day was sterile. The patient died at 7:20 a. m. on June 30.

The following note was made by Dr. A. R. Barnes on a series of electrocardiographic tracings taken on May 15 and on June 19, 23 and 29: "The initial elec-

trocardiogram taken on May 15 was within normal limits. The tracing taken at the time of the second entry, June 19, showed a decreased voltage in all leads. The tracing on June 23 showed improved voltage of the T wave of lead II and a normal fourth lead. On the morning of June 29 there appeared in the tracing a Q wave in lead III, the T wave in the same lead was inverted and T_2 became diphasic. The Q wave in the fourth lead showed less excursion, and the T wave was definitely shallower. In the tracing taken in the evening the T wave was inverted in leads II and III; a Q_3 was present. The amplitude of QR_4 was

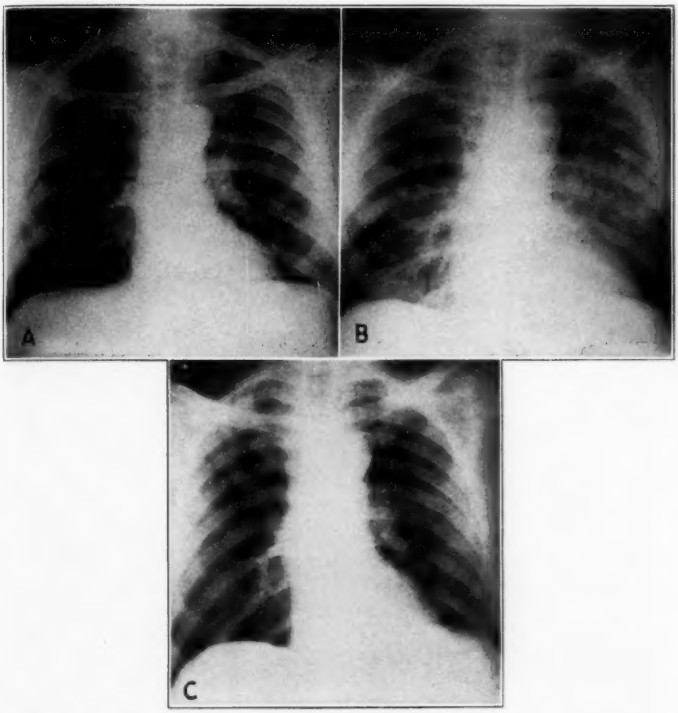

Fig. 3 (case 1).—Teleroentgenograms of the thorax taken on May 15 (*A*), June 23 (*B*) and June 27, 1936 (*C*). The first and last ones (*A* and *C*) are essentially the same. The one taken on June 23 (*B*) shows areas of congestion in both lungs.

reduced, and the T wave in lead IV was shallow or diphasic. There was nothing in these tracings suggesting either hypertension or acute coronary occlusion."

Necropsy Observations.—The outstanding pathologic changes in the vascular system were in the smaller arteries which measured approximately 100 to 500 microns in diameter and in the arterioles which measured from approximately 30 to 100 microns in diameter. The smaller arteries in many organs were diffusely inflamed, and this inflammation was seen in various stages of development. In

some instances the walls of the vessels were infiltrated with moderate numbers of lymphocytes, and a few lymphocytes had collected about the external coat. Where the process was more advanced the inflammatory reaction was more pronounced in the wall of the artery, in places leading almost to complete destruction of the muscular coat. In some vessels the subendothelial tissues were particularly invaded with inflammatory cells and were markedly thickened. This thickening occurred at the expense of the lumen, and in many instances the subendothelial inflammation had entirely obliterated it. In these vessels the Weigert stain for elastin showed the internal elastic lamina to be apparently displaced toward the periphery, so that the muscle existed merely as a thin band about the greatly thickened subendothelial layer. Where inflammation was most advanced, all the coats of the artery were destroyed, and the wall of the vessel was converted into a mass of scar tissue.

The arterioles showed changes characteristic of hypertension. The walls were thickened generally, with a resulting diminution in the ratio of the thickness of the wall to the diameter of the lumen. Thickening of the wall was due in part to an increased number of muscle cells in the medial coat. In some instances the endothelial lining appeared to be "piled up." About many arterioles there was a small region of fibrosis, and some had perivascular collections of lymphocytes. Differential stains did not show any increase in fibrous tissue in the arteriolar walls, and signs of degeneration were in general absent. Occlusion of the arterioles was not common, and the stain for elastin did not show any marked change in the elastic lamina.

The changes described in the arteries were seen in the choroid layer of the eyes, in the kidneys, heart, liver, spleen, pancreas, fibrous capsules of the adrenal glands and prostate gland and in both the large and the small bowel. The arteriolar changes described were also present in these organs, and in addition they were present in the voluntary muscles. The vessels of the lung were not markedly altered (figs. 4 to 6).

The right kidney weighed 160 Gm. and the left 178 Gm. The capsules stripped easily. There were multiple elevated yellowish areas of recent infarction on the renal surfaces, varying from a few millimeters to 1 cm. in diameter. Microscopically, thrombosed vessels were seen leading to the infarcts. Many glomeruli in noninfarcted regions were intact. There were some areas of parenchymatous degeneration of the tubules, but these were not widespread. Congo red stain did not reveal the presence of amyloid in the kidney or its vessels.

The heart weighed 460 Gm. There was sclerosis, grade 2, of the coronary arteries, but none was occluded. The left ventricle was dilated, grade 3. On microscopic examination small areas could be seen beneath the epicardial covering on the ventral aspect of the intraventricular septum, in which the cardiac muscle had been completely destroyed and replaced by loose fibrous tissue. These areas were probably small infarcts. Elsewhere the myocardium appeared to be normal. The scarlet red stain demonstrated fatty degeneration of some of the muscle fibers of the heart. Congo red stain did not reveal the presence of any amyloid.

The spleen weighed 191 Gm., and there were several small nodules of chronic tuberculosis scattered about its surface. The liver weighed 913 Gm., and numerous nodules of chronic active tuberculosis were present on its surface.

There was a small area of atelectasis in the middle of the lower lobe of the right lung, and evidence of chronic tuberculosis was seen in the lymph nodes of the hilus of the right lung. There were a few nodules of healed tuberculosis in the subpleural region of the upper lobe of the right lung.

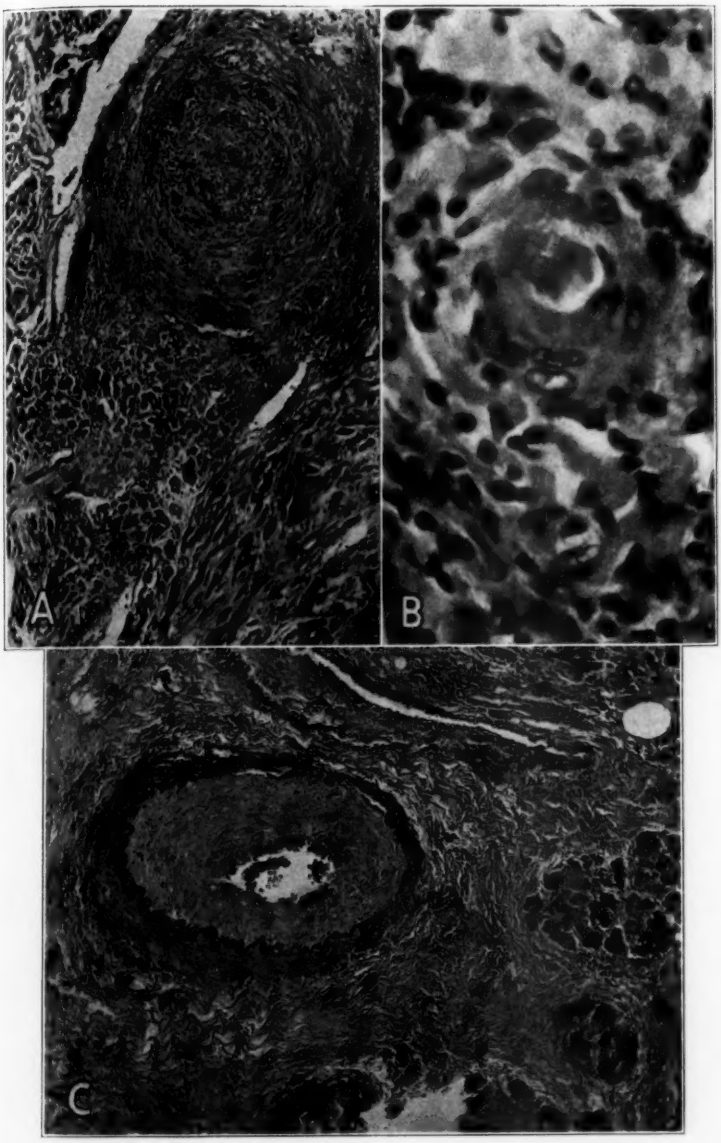

Fig. 4 (case 1).—*A*, photomicrograph of the heart showing subpericardial fibrosis. A small artery shows diffuse inflammatory changes. Hematoxylin and eosin stain; × 85. *B*, liver. An arteriole shows periarteritis with thickening of the media. Hematoxylin and eosin stain; × 750. *C*, pancreas. A small artery shows moderate inflammatory changes in the intima and media. Weigert stain for elastic tissue; × 115.

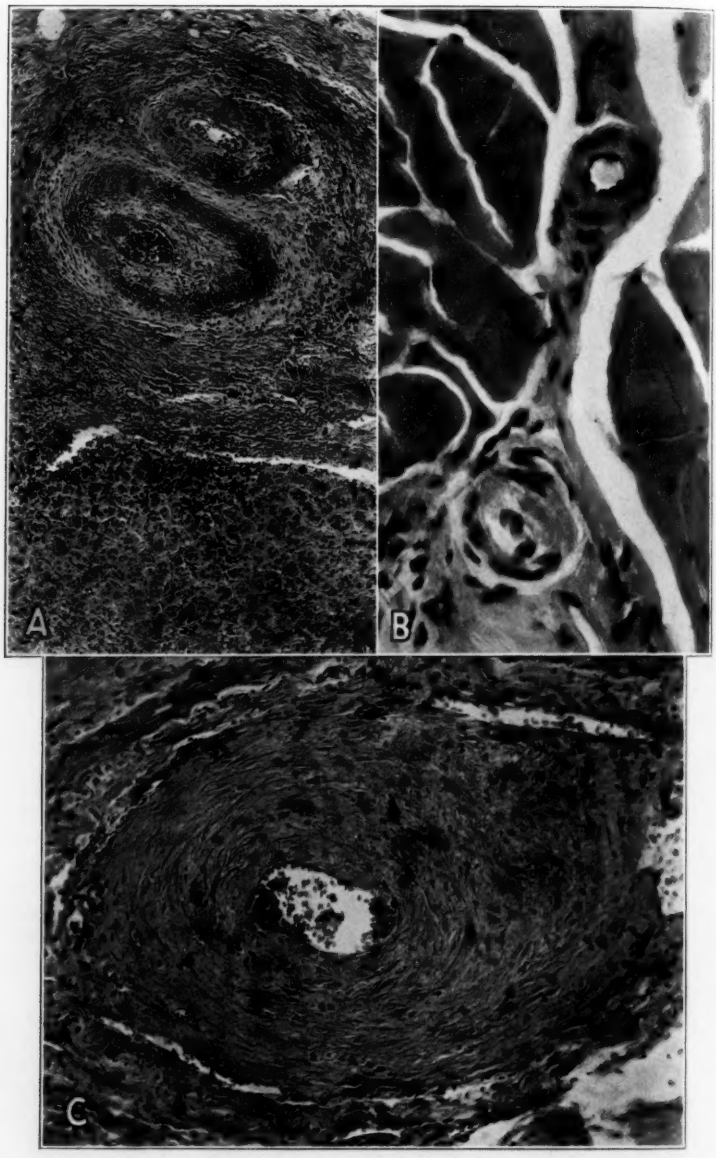

Fig. 5 (case 1).—*A*, photomicrograph of the fibrous capsule of the adrenal gland. Small arteries show replacement of all the coats by an inflammatory process. Hematoxylin and eosin stain; × 100. *B*, pectoralis major muscle. The arterioles show proliferation of the intimal endothelium, thickening of the media, periarteriolar fibrosis and an increased number of lymphocytes. Hematoxylin and eosin stain; × 500. *C*, kidney. A small artery shows mild periarteritis with fibrosis and thickening of the wall and narrowing of the lumen. Hematoxylin and eosin stain; × 185.

The pancreas weighed 100 Gm., and there was a small area of chronic tuberculosis in the tail. The aorta showed atherosclerosis, grade 2.

In each ocular bulb there were numerous small flame-shaped hemorrhages, and each retina was seen to be detached from the choroid by serofibrinous exudation. Histologically the most interesting and the only unusual finding was in the medium-sized arteries of the choroid. In approximately 20 per cent of these arteries, hyalin-like necrosis of the media was present. The hyalin-like material was fragmented and clumped into small masses, simulating the appearance in amyloid disease. It stained bright pink with eosin and did not contain any nuclei. There was no proliferation of the intima. There was slight proliferation of the adventitial connective tissue (fig. 6).

The vessels of the brain were normal except for slight thickening of the walls of the arterioles. In the vessels of the pia-arachnoid, at the bottom of some of the sulci, there were chronic inflammatory changes.

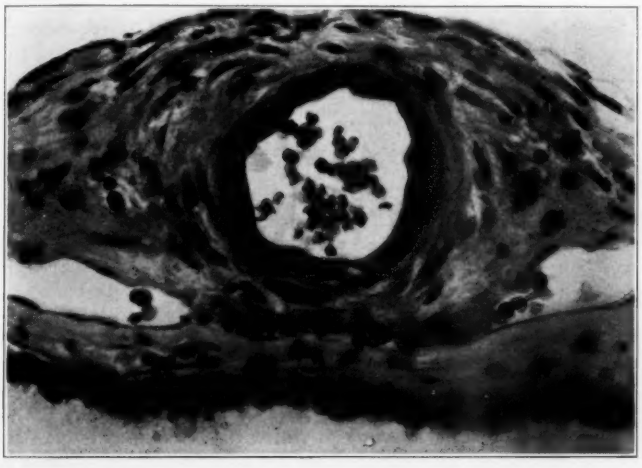

Fig. 6 (case 1).—A small artery in the choroid layer of the eye. The lumen of the vessel is irregular. The inner portion of the media shows necrosis and irregular clumps of hyalin-like material. The adventitial connective tissue shows slight proliferation. Hematoxylin and eosin stain, the tissue being embedded in photoxylin; × 435.

CASE 2.[2]—This patient, also a physician, was 49 years of age when he first came to the clinic, on Oct. 5, 1931. According to the family history, his father died of pernicious anemia at the age of 62 and his mother of hypertensive cardiovascular disease with angina pectoris at the age of 72. The patient had 3 children, living and well. He had diphtheria and scarlet fever in childhood, typhoid at the age of 17, followed by phlebitis of the left leg, and influenza during the epidemic of 1918. He underwent appendectomy at the age of 27 and tonsillectomy at the age of 39.

2. Dr. Lester J. Palmer, of Seattle, supplied many of the details of the history and course in this case and many of the pathologic data.

When the patient was 46 years old, three years before his first visit to the clinic, he began to notice occasional momentary attacks of precordial distress and slight dyspnea when he ran or when he climbed a hill. These attacks were not definitely painful, and there was no projection of the distress. Both distress and dyspnea rapidly subsided with rest. In February 1930 a competent clinician examined the patient and found "no marked abnormality of the heart, blood pressure or electrocardiogram." In September 1930 the blood pressure was again found to be normal. In September 1931 hypertension was discovered during a routine examination.

On examination at the clinic the patient weighed 210 pounds (95.4 Kg.) clothed. He was 5 feet and 11 inches (180 cm.) in height. A single determination of the blood pressure was 170 systolic and 120 diastolic. He was well nourished, and there was no anemia or edema. The pupillary reflexes were normal. The lungs were clear. The heart measured 3.5 cm. to the right and 12 cm. to the left of the midsternal line, its action was regular and there were no murmurs. There was slight accentuation of the aortic second sound, and a slight systolic heave was visible over the precordium. Abdominal and rectal examinations revealed no abnormality, and there was no gross neurologic abnormality. On palpation only slight sclerosis of the peripheral arteries was found. Vision was 6/7 in the right eye and 6/6 in the left. Examination of the ocular fundi revealed mild sclerosis (grade 1) of the hypertensive type in the retinal arterioles.

The urine at this time contained no albumin or casts. There was no anemia, the hemoglobin value being 17.5 Gm. per hundred cubic centimeters, the erythrocyte count 4,920,000 and the leukocyte count 6,800 per cubic millimeter of blood. The value for blood urea was 22 mg. and that for serum sulfates 5.7 Gm. per hundred cubic centimeters. The excretion of phenolsulfonphthalein was 60 per cent in 225 cc. of urine within two hours. The results of electrocardiographic examination at this time were reported as follows: rate, 69; sinus bradycardia; preponderance of the right ventricle; an isoelectric T wave in lead III; a lengthened Q wave in lead III, a notched QRS complex in lead II and a slurred QRS complex in leads I and III. When the blood pressure was taken hourly over a twenty-four hour period the variations were: systolic, 115 to 150, and diastolic, 70 to 110 mm. of mercury (fig. 7).

In June 1933 the patient returned for reexamination. He was then 51 years of age. He was having some extrasystoles and an occasional tight feeling across the chest. His weight had decreased to 184 pounds (83.6 Kg.). At a single determination the blood pressure was 150 systolic and 110 diastolic. The aortic second sound was accentuated, grade 2; but physical examination revealed no other changes. The patient's symptoms remained unchanged until December 1935, when for a period of several weeks he was under marked mental and physical strain. During this time he had several episodes of severe substernal distress. In some of these attacks there was definite projection of the distress to the left axilla and arm. Some alarm was felt concerning his condition, and he was placed in a hospital. He seemed to improve over a period of four weeks; but pleurisy suddenly developed on the right side, and he was confined to bed for another month. Numerous readings of the blood pressure during this period of hospitalization varied from 105 to 125 systolic and from 70 to 90 diastolic (table 2). Urinalyses showed only a trace of albumin and only an occasional cast. Determinations of certain constituents of the blood between December 25 and April 1 revealed a urea content of 43 mg., a creatinine content of 1.4 mg. and a cholesterol content of 165 mg. per hundred cubic centimeters. During this same period several examinations revealed a normal content of hemoglobin and a normal

number of erythrocytes. On March 18 a roentgenogram of the thorax revealed a moderately enlarged cardiac shadow, apparently no greater than that seen in October 1931, four and a half years previously (fig. 8).

Between Feb. 27, 1931, and March 16, 1936, ten electrocardiographic tracings were taken. Dr. Barnes has reviewed these in detail, as in the previous case, and the following is a summary of his impressions: "Right axis deviation was

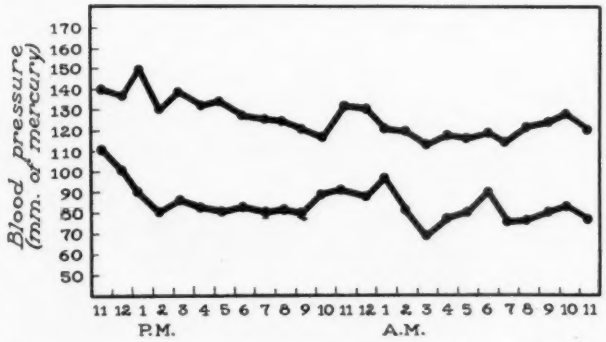

Fig. 7 (case 2).—Blood pressure readings taken over a twenty-four hour period on Oct. 7, 1931.

TABLE 2.—*Blood Pressure Readings (Case 2)*

Date	Blood Pressure, Mm. Hg	
	Systolic	Diastolic
9/25/31	180	120
10/ 5/31	170	120
10/ 7/31*		
6/ 8/33	150	110
12/28/35	125	90
1/ 2/36	125	90
1/ 9/36†	105	70
1/11/36	110	70
1/22/36	115	85
2/10/36	105	70
2/13/36	120	80
2/16/36	120	80

* Variation in twenty-four-hour period: systolic, 115 to 150; diastolic, 70 to 110.
† Hemoglobin, 13.8 Gm. per 100 cc.; erythrocytes, 4,800,000 per cu. mm.; leukocytes, 10,600 per cu. mm.

indicated in the first tracing (Feb. 27, 1931) in spite of an expectancy of left axis deviation as a result of hypertension. There was also an associated flattening or diphasic change in the T wave in lead I; however, when these changes were first observed there was no demonstrable increase in the width of the QRS complex. Tracings taken from Dec. 23, 1935, until March 16, 1936, revealed evidences of bundle branch disturbances, indicated by an increasing width of the QRS complex as well as notching or slurring or both. A detailed study revealed that first the left and later the right bundle branches were involved. At no time was the bundle branch defect complete, and in general it seemed of moderate degree.

In view of the subsequent changes in the QRS complex it seems reasonable to assume that the bundle branch injury accounted for the earliest changes. All these changes may be interpreted as a result of sclerosis in the coronary arteries supplying the bundle branches. The tracings gave no evidence at any time of acute coronary occlusion."

In March the patient gradually became more active and resumed part-time work. The urine continued to be free from albumin and casts. Several ophthalmoscopic examinations were made subsequent to Oct. 6, 1931, the last being made on April 20, 1936. There was always slight sclerosis of the retinal arterioles, but at no time was there any evidence of retinitis.

On April 6, 1936, the patient drove his car home from his office in the evening and as he alighted noticed numbness of the left foot. He thought that slight pressure on a nerve had resulted from his position while driving. This numbness increased, however, and after an hour he called a colleague, who discovered marked pallor of the leg and absence of pulsations from the vessels below the femoral

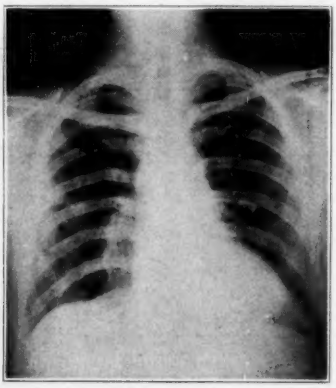

Fig. 8 (case 2).—Teleroentgenogram of the thorax, March 18, 1936.

artery. There was no pain. On April 8 the patient was found semiconscious, with complete left hemiplegia. From April 16 to 26 he had hiccup. His left foot then became gangrenous, and on May 2 amputation was performed through the midportion of the thigh. Histologic examination of a medium-sized artery from the amputated leg revealed marked destruction of the medial coat, with extensive deposits of calcium and atheromatous formation. There was thrombosis with beginning organization which completely occluded the lumen of the vessel (fig. 9 *A*). There was ancient thrombosis of the accompanying vein, which was entirely organized and contained numerous canals.

On May 6 pulsations disappeared from the vessels of the right leg, and shortly after this it became evident that there was blockage of the circulation to the sacral, gluteal and lower lumbar regions. In this region a large infected decubital ulcer developed. The patient slowly became weaker and died on June 20.

Necropsy Observations.—At necropsy the lining of the upper half of the aorta showed marked atherosclerosis, approximately 65 per cent of the lining being involved. Immediately below the origin of the renal arteries the aorta was com-

pletely occluded by a large organized thrombus which extended peripherally into both iliac arteries. There was a large antemortem thrombus in the lower portion of the inferior vena cava, approximately 12 cm. in length.

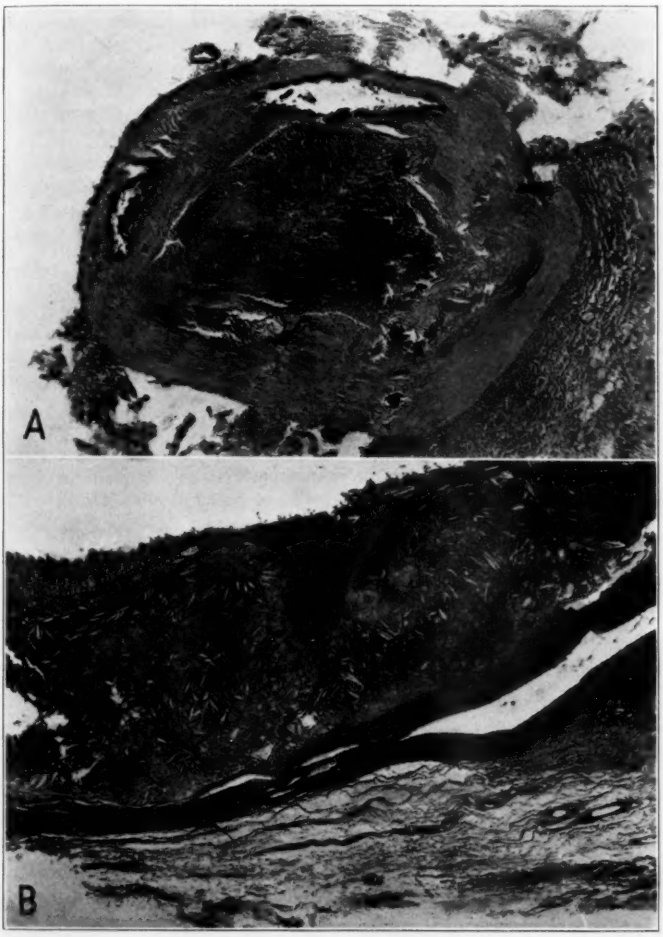

Fig. 9 (case 2).—*A*, an artery of the left leg, showing thrombosis and deposits of calcium in the arterial wall. Hematoxylin and eosin stain; × 30. *B*, the abdominal aorta, showing atheromatous plaques containing cholesterol crystals. Hematoxylin and eosin stain; × 20.

The heart weighed 525 Gm. There were moderate hypertrophy of the wall and dilatation of the chamber of the left ventricle. There was moderate to marked

atherosclerosis of the coronary arteries but no gross scarring of the myocardium. The kidneys together weighed 350 Gm. The capsules stripped easily, and they were architecturally well preserved. Also present were bronchopneumonia and purulent tracheobronchitis, with multiple infarcts in the spleen. The brain was not examined.

Microscopic examination of the aorta showed marked irregular narrowing and destruction, with fibrosis of the arterial wall. Large areas of the vessel showed atheromatous formation with cholesterol clefts. There was some deposition of calcium in the atheroma. Numerous areas of lymphocytes were scattered through the wall and in the adventitia. The picture was that of advanced atherosclerosis (fig. 9*B*).

A section of the vena cava at the level of the thrombus showed almost complete occlusion, with numerous histiocytes and some blood pigment in the margin of the clot. The clot was adherent to the wall of the vein. The wall contained a moderate number of fibroblasts and a few lymphocytes. These findings indicated nonspecific thrombophlebitis, several weeks or even a few months old.

The cardiac muscle showed some variation in the size of the nuclei. One definite area of fibrosis was seen, but this was not extensive. There was some increase in the fibrous tissue between muscle fibers, and the small veins and venules appeared to be dilated. Arterioles appeared normal. These observations possibly indicated some chronic infarction and fibrosis of the myocardium, but there were insufficient sections to be certain of either.

In the liver some congestion was seen around the hepatic veins. Some fatty infiltration of the parenchyma was present, but the blood vessels were esentially normal. The lungs showed patchy bronchopneumonia and bronchitis of the small and terminal bronchioles. The pulmonary vessels were not abnormal.

COMMENT

Clinical Course.—The complex nature of diffuse arterial and arteriolar disease is exemplified in these 2 cases. In case 1 the course was rapid, the hypertension sustained and the terminal phase explosive. The final clinical manifestations were due to marked dysfunction of the retina, choroid, central nervous system, heart and kidneys. We have noted previously a similar but more slowly developing terminal syndrome in so-called malignant hypertensive disease. A logical interpretation of such findings is that there is a simultaneous interference with the blood supply to these vital organs due either to acute vasospasm or to acute or chronic pathologic lesions in the majority of the arterioles. These and other facts indicate that there is a close relation between diffuse arteriolar dysfunction and hypertension. Of added interest in the first case was the history of initial fever and of fever during the last week of life together with polymorphonuclear leukocytosis. These clinical evidences of toxemia and the presence of inflammatory-like lesions in the small arteries suggest the possibility that the vascular disease was of infectious or toxic origin.

The relatively slower clinical course, the periods of comparatively good health and the mild hypertension in case 2 were associated with

the development of atherosclerotic lesions in the arteries. The terminal clinical picture was due to the development of thromboses in the vicinity of the atheromatous lesions. Strange as it may seem, actual coronary thrombosis did not occur. The moderate and fluctuating hypertension was probably due to a slight and nonprogressive disturbance of the arterioles.

Retinal Picture.—The retinal change seen in case 1 was of the type which is usually spoken of as typical of "albuminuric retinitis"; it was characterized by diffuse edema of the retina and of the optic nerve, with various hemorrhagic and exudative lesions and with visible changes in the retinal blood vessels. This retinitis is often considered to be primarily nephritic in origin. Of course, renal insufficiency may develop at the same time or soon after retinitis of this type, but the development of renal insufficiency may be delayed for a long period after the development of the retinitis. It is therefore improbable that the renal insufficiency in itself has any influence on the production of retinitis of this character. Retinitis rarely develops in these cases without the development coincidentally or previously of a considerable elevation of the blood pressure. A rapid elevation of blood pressure is usually accompanied by generalized and irregularly distributed localized narrowings in the arterioles of the retina. These arteriolar changes usually precede the retinitis. Since it is usually impossible to find histologic counterparts for these clinically visible irregularities in the arterioles, we like to consider this type of retinitis as angiospastic, especially since the changes in the vessels develop rapidly and may disappear rapidly and spontaneously.

In case 1 evidence of general and irregular narrowing of the arterioles in the retina was extreme, particularly in some of the smaller branches of the arterioles, and this narrowing developed rapidly, certainly within a few weeks. These retinal changes suggested that there was a rapidly developing lesion of the small arterioles throughout the body. In addition to the usual lesions of angiospastic retinitis, subretinal edema was present in amounts sufficient to detach the retinas measurably. The source of this edema was probably the vascular lesions in the choroid which we originally interpreted, possibly incorrectly, as being angiospastic. In any event, the presence of these lesions suggested that the vascular disease was even more widespread and that it involved larger vessels than are affected in the usual case of vasospastic hypertension. This widespread distribution and unusual nature of the lesions in the small arteries and arterioles were demonstrated at necropsy.

In contrast with the observations in case 1, the retinal changes in case 2 were minimal. They consisted of mild arteriovenous compression

and mild narrowing of the retinal arterioles; also present was a slight change in the color of the arterioles. These ophthalmoscopic signs are interpreted by some to represent an increase of vasomotor tone in the arterioles, but we like to think of them as indicating a mild thickening of the media residual to a mild angiospastic episode, similar in type but less severe in degree than that seen in acute vasospastic hypertension. In cases of this type in which the angiospastic episodes do not recur, these retinal changes will remain constant for years, as they did in this particular case. Examination of the retina in this case during the last few months of the patient's life still showed mild sclerosis of the retinal arterioles, in spite of the fact that the blood pressure had returned practically to normal. In patients with mild hypertension and marked sclerosis of the larger arteries, the changes in the choroid arteries are more marked than those in the retinal arterioles. Sclerosis of the choroid arteries occurs quite regularly with increasing age, and it can often be demonstrated histologically when it has not been noted clinically. When sclerosis of the choroid vessels develops prematurely, between the ages of 45 and 60 years, it is usually associated with atherosclerosis of the larger vessels of the body and often with coronary sclerosis. In this particular case we are not able to say whether there was a definite histologic thickening of the choroid arteries because the eye was not available for histologic study.

Pathologic Changes.[3]—In 1928 Kernohan and two of us (Drs. Keith and Wagener) [4] reviewed a series of cases of so-called malignant hypertension. The fact was stressed that in these cases the diffuse arterial disease not only involved the vessels of the kidneys but affected many of the arteries and arterioles throughout the body. Since then we have applied the term diffuse arterial disease to similar conditions, but we realize that it is a broad term and should include unique examples, such as in the present cases. In case 1 the diffuse vascular process had distinctive features which were different from those in so-called malignant hypertension and also from those observed in case 2.

At necropsy in case 1 the most significant gross finding was the presence of visible multiple infarcts on the surface of the kidneys. These infarcts produced a condition essentially that of symmetric cortical necrosis, the type of necrosis usually present in cases of severe eclamptic toxemia.[5] The development of these infarcts readily explained

3. Dr. J. W. Kernohan assisted in interpreting the pathologic changes in these cases.

4. Keith, N. M.; Wegener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141-188 (Feb.) 1928.

5. Evans, N., and Gilbert, E. W.: Symmetrical Cortical Necrosis of the Kidneys: A Report of a Case, Am. J. Path. **12**:553-560 (July) 1936.

the sudden appearance of large numbers of erythrocytes in the urine and the subsequent rapid failure of renal function. It was also significant that detachment of the retina and hemorrhages within its structure could be seen with the naked eye. On histologic examination there were few if any pathologic alterations in the retinal arterioles, but there were marked changes in some of the choroid arteries. These microscopic observations corroborated the previous ophthalmoscopic findings. The presence of small scattered areas of chronic tuberculosis did not seem significant etiologically with regard to either the vascular lesions or the presence of hypertension. On the contrary, it has long been claimed that chronic pulmonary tuberculosis is accompanied by hypotension. Mention should also be made of the absence of histologic changes in the retinal and intracerebral arteries and arterioles. Such negative evidence of organic disease strengthens the supposition that angiospasm is an important factor in causing the serious retinal and cerebral symptoms.

Ten years ago Kernohan, Anderson and one of us (Dr. Keith) [6] began to measure the diameter of the arterioles in diffuse arterial disease, as no previous systematic attempt had been made to ascertain the normal ratio between the thickness of the wall and the diameter of the lumen. They found the normal ratio in the arterioles of voluntary muscle to be approximately 1:2, and in many cases of serious arterial disease the ratio was reduced even to 1:1. The arterioles in the pectoral muscle in case 1 showed marked thickening, chiefly of the media, and the ratio of the thickness of the wall and the diameter of the lumen was about 1:1. We have considered this hypertrophy of muscle as being secondary to strain and possibly to the hypertension. Many arterioles of various organs throughout the body showed a similar lesion. However, the smaller arteries in many organs revealed other types of pathologic change. In a small artery of the pancreas the intima was greatly thickened, the intimal cells being "piled up" and the media almost destroyed. On the other hand, a small artery in the heart revealed almost complete obliteration, with periarteritis around it and enlargement of many of the nuclei within its wall. The occurrence of this periarteritis, an inflammatory-like change, in many widely distributed small arteries in case 1 and in arteries of corresponding size in the kidneys in 2 cases of severe hypertension reported by Klemperer and Otani [7] suggested a similarity to the lesion in periarteritis nodosa.[8]

6. Kernohan, J. W.; Anderson, E. W., and Keith, N. M.: The Arterioles in Cases of Hypertension, Arch. Int. Med. **44**:395-423 (Sept.) 1929.

7. Klemperer, P., and Otani, S.: "Malignant Nephrosclerosis" (Fahr), Arch. Path. **11**:60-117 (Jan.) 1931.

8. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa, Arch. Neurol. & Psychiat. **39**:655-686 (April) 1938.

These lesions in our case 1 would possibly explain the presence of fever and leukocytosis and also the severe pains in the legs and arms. There is still, however, much mystery regarding the primary cause of periarteritis nodosa.

The hyalin-like necrosis of the media of some of the choroid arteries was regarded by Dr. Kernohan as representing the earliest phase in the development of the lesions of periarteritis nodosa. It is of interest in the case of periarteritis nodosa with "albuminuric retinitis" described by Friedenwald and Rones [9] that the periarterial lesions were present in the choroid but not in the retina and that they were in a well developed, almost terminal stage. Friedenwald said he considered that the retinitis was due to the arteriolosclerotic lesions in the retina, which were identical with those seen in the usual case not associated with periarteritis nodosa. In our case 1, death occurred too rapidly for arteriolosclerosis to develop in the retina, but we feel justified in attributing the retinitis proper to the spastic constriction of the retinal arterioles rather than to the early inflammatory lesions in the vessels of the choroid.

It is much easier to explain the pathologic picture in case 2 than that in case 1. The fundamental change in case 2 was that of arteriosclerosis, and histologic sections of the abdominal aorta showed all the typical features of this condition, including calcified areas, ulceration and cholesterol crystals.

At this juncture several facts regarding arteriosclerosis are worthy of consideration: First is the question of age. One naturally expects to encounter arteriosclerosis in elderly persons. It may, however, begin in children and gradually progress through life. In some instances the disease progresses slowly, but in others it begins early and progresses relatively rapidly and leads to the results seen in our case 2. Heredity probably plays a role in the occurrence of arteriosclerosis, but exact data for the proof of such an assumption are lacking. Aschoff [10] claimed that atheromatous deposits in the arteries are frequently associated with, and possibly secondary to, a high cholesterol content of the blood. In our case 2 the cholesterol concentration of the plasma was within the normal range, so that hypercholesteremia is not always demonstrable. This is in agreement with the findings of Duff.[11] Finally, there is little direct evidence of an exact relation between arteriosclerosis and hypertension.

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9. Friedenwald, J. S., and Rones, B.: Some Ocular Lesions in Septicemia, Tr. Am. Ophth. Soc. **28**:286-300, 1930.

10. Aschoff, L.: Lectures on Pathology, New York, Paul B. Hoeber, 1924.

11. Duff, G. L.: Experimental Cholesterol Arteriosclerosis and Its Relation to Human Arteriosclerosis, Arch. Path. **20**:81-123 (July); 259-304 (Aug.) 1935.

CONCLUSIONS

The term diffuse arterial disease when used in a broad sense includes cases in which there are primary changes both in the arteries and in the arterioles. Two contrasting cases are reported in which the preponderant alteration in 1 was in the arterioles, whereas in the other it was in the arteries. The general conclusion is drawn that in patients with sustained hypertension, the site of the predominating change, whether it is an abnormal physiologic process or an actual anatomic lesion, is in the arterioles; on the other hand, in patients with diffuse atherosclerosis of the arteries, hypertension is often mild and fluctuating or even absent.

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A CRITICAL REVIEW OF THE SURGICAL TREATMENT

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A REVIEW OF SOME OF THE RECENT LITERATURE

By Dr. Scupham and Dr. Van Dellen

In the past year the importance of general involvement in the course of vascular diseases has been emphasized by a number of writers. In association with this idea, primary vascular hypertension has been occupying a much larger place in investigative interest. For this reason a brief résumé of some of the work on this subject will be included in this review.

No attempt will be made to discuss all the papers which have been published, but certain ones have been selected which seem to be contributions to the knowledge of vascular diseases. In some instances material has been included which has been covered, at least in part, in previous reviews. This has been done because the subject seems to bear the emphasis of repetition without becoming commonplace.

PHYSIOLOGY

In the annual George E. Brown lecture, Cannon [1] reviews the factors affecting vascular tone. The term is used to designate a state of moderate contraction of the elements in the walls of the blood vessels. This state may be decreased or increased by the operation of various factors. In discussing the effect of sympathectomy he quotes the evidence which indicates that vascular tone returns to an approximate normal level after

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1. Cannon, W. B.: Factors Affecting Vascular Tone, Am. Heart J. **14**:383, 1937.

sympathectomy in animals. After local section of the vasoconstrictor nerves the blood vessels regain their normal tone in a variable length of time. Cannon states that the evidence is clear on this point. After complete denervation of the sympathetic nerves there is eventually a return of the blood pressure to approximately the normal level after a short interval. The restoration of the blood pressure level after sympathectomy may be partly due to an increase in the volume of blood. The effect of section of the sympathetic nerves on smooth muscle, rendering it more sensitive to epinephrine, is considered in detail in Cannon's discussion. That this effect is not due solely to the effect of epinephrine is pointed out. The substance sympathin must be considered. It is discharged into the blood stream under the same conditions as is epinephrine, that is, with emotional excitement, hypoglycemia, cold, pain and vigorous muscular activity. It is probable that both sympathin and epinephrine collaborate in producing this effect. Whether or not there is another gland of internal secretion which supplies the chemical agent that might act for the restoration of tone in sympathectomized vessels is not known. It is likewise not certain that any hormonal substance is necessary for the restoration of tone. Cannon believes that this may be regarded as an intrinsic property of smooth muscle itself. The variations in blood flow which have been observed after the application of heat to denervated vessels may be determined by the metabolic needs of the tissues or may be the consequence of the change of temperature in the vessels themselves.

That smooth muscle may be relaxed by nerve stimulation has long been known. In the completely sympathectomized animal there is a fall in blood pressure after vigorous muscular activity. This has been explained as an effect of muscular metabolites on the vessels, producing vasodilatation. Cannon states that this occurs too rapidly to be explained on this basis. There is evidence which supports the view that there is actually a vasodilator center in the floor of the fourth ventricle. It is probable that the route by which impulses reach the periphery after a stimulus in completely sympathectomized animals is through the dorsal roots.

There are three explanations for the production of excessive tone such as that which occurs in hypertensive states. One is the excessive discharge of vasoconstrictor impulses from the central nervous system. An abnormal narrowing of the vascular channels might be produced in such a manner. Evidence for this is the hypertension which develops after all the restraining nerves are severed. These are the cardioaortic and carotid sinus plexuses. The second condition is that blood vessels, even though normally innervated, may become especially sensitive to natural stimuli, much in the manner of the paroxysm in Raynaud's disease. The third way in which general vasoconstriction might develop

is through peripheral stimulation of the smooth muscle by unusual chemical agents. This is still an unknown factor.

Blood Cholesterol.—The relation of lipoid metabolism to vascular diseases has been discussed in previous reviews. Alterations in the cholesterol content of the blood have been reported by various observers.

Jacobi,[2] in treating diseases of this type with intravenous injections of solutions, noted rather marked changes in the cholesterol values of the blood. He and his associates employed solutions of 2 per cent sodium iodide in physiologic solution of sodium chloride or 2 per cent solution of sodium chloride. Most of the patients whom they treated had painful ulcerative lesions of the extremities. During the course of treatment the only significant changes noted in chemical studies of the blood were in the cholesterol levels. Before treatment these values were either subnormal or in the low normal range. After the use of chloride or iodide solutions for a short time a sharp rise in the cholesterol value was invariably noted. This was followed by a subsequent fall to the normal level as treatment was continued. In some instances the height of the cholesterol response amounted to almost three times the initial figure. It was also noted that the lower the initial cholesterol value, the more marked the relief from pain and the more rapid the healing process after the introduction of this type of treatment. For those patients in whom the disease recurred after treatment, the cholesterol level was again found to be lowered. This decrease was found to occur before the return of pain or ulceration. The mechanism of this response is still uncertain, and further observations should be made to throw light on what may be an important feature of obstructive vascular disease.

Plethysmographic Studies.—Several types of plethysmographs have been used for the study of circulation. Turner[3] has devised an instrument of this type for the measurement of the changes in volume due to pulsation in a portion of the finger. The apparatus makes a graphic record of pulse volumes as small as 0.1 cu. mm. and of gradual changes in volume as great as 1,000 cu. mm. A series of studies with this device have been reported.

Sodeman[4] describes a method for estimating the volume of soft tissues in the portion of the finger used with this instrument. This

2. Jacobi, H. G.: The Blood-Cholesterol Response to Intravenous Therapy in Peripheral Arterial Disease, Am. J. M. Sc. **193**:737, 1937.

3. Turner, R. H.: Studies in the Physiology of Blood Vessels in Man: Apparatus and Methods: I. A Sensitive Plethysmosphygmograph for a Portion of the Finger, J. Clin. Investigation **16**:777, 1937.

4. Sodeman, W. A.: Studies in the Physiology of Blood Vessels in Man; Apparatus and Methods: II. A Method for the Determination of the Volume of the Soft Tissue About the Terminal Phalanx of the Human Finger, J. Clin. Investigation **16**:787, 1937.

consists of measuring the total volume, estimating the volume of bone and subtracting the latter from the former. With this apparatus Turner, Burch and Sodeman [5] have made some observations on the effects of raising and lowering the arm on the pulse volume and blood volume of the finger tip in normal persons and in a few patients with vascular diseases. A change in pulse volume was found in all instances with a change in the level of the hand. The pulse volume increased with the elevated position and decreased with the lowered position, while the blood volume of the finger tip varied in the opposite way in most instances. In subjects with arteriosclerosis only, the mean volume of pulsation was approximately the same as that in normal subjects, while the mean total blood volume of the finger part was less. In instances of diastolic hypertension the volume of pulsations and the total blood volume were measured with the hand at the level of the heart, and it was found that with an elevated position these values were reduced. The total blood volume was essentially normal, but the pulsation volume was diminished. With the hand 45 cm. below the level of the heart the total blood volume was reduced, but the volume of pulsation was similar to that for the normal group. In 1 subject with a localized Raynaud phenomenon with atrophic changes in the left index finger, distinct changes were noted in comparison with the corresponding normal finger of the other hand. The involved finger showed a reduced total volume of blood in all positions that was out of proportion to the reduction in the total volume of soft tissues. The volume of pulsations was slightly reduced at the cardiac level and definitely so in both the elevated and the lowered position. The changes in all instances, they believe, are due to actual change in the relation of the volume of blood to the volume of soft tissues. The pulse wave is manifested by changes in volume in those vessels which contribute most to the color of the skin, and these vessels are dilated in the depressed and narrowed in the elevated position. These vessels are the capillaries and venules. The increase in the total volume of blood in the fingers in the depressed position and its diminution in the elevated position, they believe, are due to changes in the caliber of the veins and occur in spite of changes in the opposite direction in the arterial vessels. They state that in normal subjects there seems to be no significant correlation between pulse pressure and pulse volume. The influence of position on pulse volume they ascribe to changes in the distensibility of both

5. Turner, R. H.; Burch, G. E., and Sodeman, W. A.: Studies in the Physiology of the Blood Vessels in Man: III. Some Effects of Raising and Lowering the Arm upon the Pulse Volume and Blood Volume of the Human Finger Tip in Health and in Certain Diseases of the Blood Vessels, J. Clin. Investigation **16**:789, 1937.

arterial and venous vessels and to changes in smoothing effect on the pulse wave. The same authors studied the changes in volume following sudden occlusion. They observed not only primary swelling of the finger following sudden occlusion but also a spontaneous secondary diminution in volume. This occurred only when pressures between 40 and 50 mm. of mercury were employed for occlusion. If pressures above this level were used, only swelling occurred. They believe these reactions are due to the distention of the small veins and capillaries and the subsequent loss in volume due to active constriction of these vessels. This is probably initiated as a response to the increased tension in these vessels.

Hertzman [6] reports an interesting method for estimating the amount of blood in the fingers and toes by means of a photoelectric cell. This device is attached to the string galvanometer of an electrocardiograph, and variations in the volume of blood in the part are recorded by the camera of the instrument. The form of the records produced conforms, in general, to the transmission type of plethysmograph and lends itself well to clinical use in the dynamic analysis of the peripheral circulation. Apparently this method may be used to study the effects of various procedures on digital pulse volume as well as the form and amplitude of the pulse volume of the fingers or toes. In a comparison of the effect of amyl nitrite on pulse volume the results were similar to those obtained with an optically recording plethysmograph. This interesting method of studying the peripheral blood vessels has been applied by the author to the nasal septum and apparently may be used in many other portions of the body. The method seems valuable and certainly should be useful in studying qualitative changes.

Ratschow [7] describes a simple ergometer with which, he believes, considerable information may be obtained. This apparatus not only will aid in determining the efficiency of the arterial supply to the muscles in cases of early vascular disease but will serve to differentiate other forms of pain in the extremities which may be easily confused with the pain of vascular impairment. It is likewise a method by which information can be gained entirely on an objective basis as to the progress and effect of therapy. He points out that while rest is essential in the treatment of such disorders in cases in which the condition is progressing to healing, limited exercise may be given if this apparatus is used. The apparatus can be quantitatively adjusted so that no harm

6. Hertzman, A. B.: Photoelectric Plethysmography of the Nasal Septum in Man, Proc. Soc. Exper. Biol. & Med. **37**:290, 1937; Photoelectric Plethysmography of the Fingers and Toes in Man, ibid. **37**:529, 1937.

7. Ratschow, M.: Der Arbeitsversuch, eine einfache Methode zur Erkennung und Berteilung peripherer arterieller Durchblutungsstörungen, München. med. Wchnschr. **84**:1128, 1937.

will be done if the amount of exercise is restricted to a point less than that which will produce pain or discoloration of the extremity.

Intra-Arterial Injection of Drugs.—Allen and Crisler [8] studied the effect of the intra-arterial injection of papaverine hydrochloride, acetyl-betamethylcholine chloride and histamine phosphate on the peripheral cutaneous temperature. The temperature of the fingers in all instances rose to a much higher degree than did that of the toes. This occurred regardless of the location of the injection, whether given in the femoral or in the brachial artery or whether given intramuscularly or intravenously, when papaverine was given. It was found impossible to fix a drug of this type in any extremity. The lower extremities seem to be relatively refractory to such vasodilating drugs. They believe that the refractoriness of vasodilatation of the lower extremities is intimately associated in some, as yet unexplained, way with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted to their incidence in the upper extremities.

In studying the effect of epinephrine on the digital arterioles of man, Fatherree and Allen [9] found that the demonstration of the vasoconstrictor effect on the digital arterioles was dependent on the presence of sufficient vasodilatation preceding the experiment. Even when vasodilatation was present, the injection of epinephrine hydrochloride intravenously, according to the method of Freeman, Smithwick and White, did not always cause significant vasoconstriction in persons with normally innervated extremities. The vasoconstrictor effect of this drug varies widely in different persons. There was even marked variability of response in the same individual at the same temperature. So much variation was encountered that the response of the temperature of the skin did not seem to be a reliable estimate of the effect of the drug. According to the writers, patients with vasomotor symptoms suggesting Raynaud's disease do not have arterioles which are unduly sensitive to epinephrine. Those persons in whom the reaction demonstrated that the arterioles were more than usually sensitive had no evidence of vasomotor disease. The authors do not believe that the recurrence of vasomotor symptoms after ganglionectomy for Raynaud's disease can be due to increased sensitivity of the arterioles to epinephrine.

On the basis of the effect of sodium nitrite on the peripheral vascular bed,[10] this drug has been employed in testing the flexibility and integrity

8. Allen, E. V., and Crisler, G. R.: The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation: Observations on Vasomotor Gradient, J. Clin. Investigation **16**:649, 1937.

9. Fatherree, T. J., and Allen, E. V.: The Influence of Epinephrine on the Digital Arterioles of Man: A Study of the Vasoconstrictor Effects, J. Clin. Investigation **17**:109, 1938.

10. Beck, W. C., and de Takáts, G.: The Use of Sodium Nitrite for Testing the Flexibility of the Peripheral Vascular Bed, Am. Heart J. **15**:158, 1938.

of the peripheral arteries, 0.04 Gm. of freshly dissolved sodium nitrite in water being injected intravenously. Before the injection is made an oscillometric curve is obtained. The effect of the drug becomes apparent in ten or fifteen minutes, after which time a second oscillometric curve is obtained for comparison with the original. No significant fall in blood pressure occurs with the amount of the drug used. The writers believe that the drug acts primarily on the terminal arteries with a secondary arteriolar constriction in order to maintain the blood pressure. Even patients with marked hypertension show no significant fall in blood pressure. The capacity for maximum vasodilatation depends chiefly on the amount of organic damage present.

Killian and Oclassen [11] made some observations on the relative effects of water baths and mustard baths at varying temperatures on the rate of peripheral blood flow. Observations were made by means of a plethysmograph. Water baths at 38 and 40 C. had a definite effect in increasing the blood flow in both the hands and the feet. When 6 per cent of mustard was added, the rate of blood flow increased as much as 74 per cent above that when water alone was used at these temperatures. Cooling the surface of the skin reduced the rate of blood flow. At temperatures of 25 to 30 C., mustard baths did not affect the rate of blood flow in the foot more than did the water bath at the same temperature. At temperatures between 35 and 40 C. the mustard bath did increase the rate of blood flow from 17 to 69 per cent above the average rates of flow in water baths at these temperatures. Above 40 C. there was relatively little difference whether mustard was added to water or not.

Capillaries.—Bordley, Grow and Sherman [12] report some interesting observations on the capillaries of the skin of the leg. These observations indicate that the flow of corpuscles through individual capillaries of the human skin is controlled by a mechanism residing in the capillaries themselves under normal conditions. The circulation through individual capillaries is frequently intermittent; in fact, intermission in flow may occur alternatively in capillaries arising from the same arteriole. When the flow ceases in a capillary, the vessel may become completely empty of corpuscles. These findings indicate confirmation of the views previously reported that capillaries have an individual function in regulating the flow of blood through them.

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11. Killian, J. A., and Oclassen, C. A.: Comparative Effects of Water Baths and Mustard Baths at Varying Temperatures on the Rate of Peripheral Blood Flow in Man, Am. Heart J. **15**:425, 1938.

12. Bordley, J., III; Grow, M. H., and Sherman, W. B.: Intermittent Blood Flow in the Capillaries of Human Skin, Bull. Johns Hopkins Hosp. **62**:1, 1938.

Springorum [13] emphasizes the importance of the blood vessels of the skin as far as their effect on the circulatory system is concerned. This relation is particularly important in regard to the injection of vasodilator drugs when the shift of blood to these vessels may be great enough to bring about collapse. Important variations may occur in association with changes in temperature, so that under certain conditions even changes in arterial blood pressure may result.

Temperature of the Skin.—Sheard, Williams and Horton [14] have studied the role of the extremities in the exchange of energy between the normal human body and its environment. They conducted experiments under controlled conditions and recorded the temperature of the skin in various locations. They found that the surfaces of the head and trunk play only a small part in the regulation of body temperature, that is, in the maintenance of the balance between internal heat production and heat elimination. The upper portions of the arms and legs maintain a fairly uniform range of temperature, from 30 to 35 C. The lower portions of the extremities play the main role in regulating body temperature through a much greater shift of blood and an increased flow to the skin. When the body is exposed to room temperatures at 60 to 65 F. the temperature of the fingers and toes tends to approach that of room temperature. As the room temperature is raised the amount of heat dissipated is increased. At higher environmental temperatures the temperature of the fingers approaches that of the head and trunk. With increased internal heat production the extremities show a rise in temperature and play an important part in heat elimination. Persons with peripheral vascular disease do not show the same heat control pattern that normal persons show.

Friedlander, Silbert, Bierman and Laskey [15] have made some interesting observations on the relation between the temperature of the skin and the temperature of the muscles of the lower extremities under certain conditions. The application of heat to the upper extremities, according to the method of Landis, produced striking elevation in the temperature of the skin of the feet, but the temperature of the muscles of the legs remained unchanged. Similar observations were made after the paravertebral injection of procaine hydrochloride. Spinal anesthesia was followed by marked elevation of the temperature of the skin, while

13. Springorum, P. W.: Die Bedeutung der Hautgefässe für den Gesamtkreislauf, Klin. Wchnschr. **17**:11, 1938.

14. Sheard, C.; Williams, M. M. D., and Horton, B. T.: The Exchange of Energy Between the Normal Human Body and Its Environment: I. The Role of the Extremities, Proc. Staff Meet., Mayo Clin. **13**:13, 1938.

15. Friedlander, M.; Silbert, S.; Bierman, W., and Laskey, N.: Differences in Temperature of Skin and Muscles of the Lower Extremities Following Various Procedures, Proc. Soc. Exper. Biol. & Med. **38**:150, 1938.

the temperature of the muscles remained unchanged. Intravenous injection of hypertonic solutions of sodium chloride was followed by elevation of the temperature of both skin and muscles. Intramuscular injections of extract of pancreatic tissue were not followed by any change in the temperature of the skin or muscles. Intravenous injections of epinephrine hydrochloride produced a striking rise in the temperature of muscles which had a good circulation and produced a fall in the temperature of the skin when the circulation was impaired. The increase in the temperature of the muscles was less marked. They point out that the usual assumption that an increase in the temperature of the skin is an indication of increased circulation is apparently not true as far as the blood supply to the muscles is concerned. The failure of various methods of increasing the temperature of the skin to relieve intermittent claudication is explained by these conditions.

Collateral Circulation.—Some interesting experiments have been reported by Stein [16] on the development of collateral circulation in the ear of the rabbit after ligation of the main arteries. An extensive collateral circulation developed within a few days. Instead of the normal regular, definite pattern, that of the collateral circulation was irregular and aimless. The vessels were increased in number; they were tortuous and varied widely in size. The circulation was adequate to meet the needs of the tissue, and most of the vascular reactions were normal except when ligation was made low.

Under controlled conditions these ears were subjected to treatment with positive and negative pressure. In the ears so treated vascular spasms occurred, and cyanosis became marked. Anoxemia developed which finally resulted in necrosis.

In an arteriographic study of the vessels in the lower extremities of patients who had suffered occlusion of large arteries, Yater [17] was able to visualize the method by which the collateral circulation developed. The occluded portions of the vessels were seen to be bridged across by long, fine, irregular branches so that the lumen of each vessel above the point of occlusion was connected with that below. The function of the main artery was thus reestablished. The number, character and size of the collateral channels seemed to vary considerably. Most collateral vessels seemed to be enlarged and elongated branches that existed before the onset of vascular disease. New anastomoses probably developed, since, as the author indicates, it is unlikely that a branch of an

16. Stein, I. D.: Studies of the Collateral Circulation Following Experimental Vascular Occlusion, Am. Heart J. **14**:726, 1937.

17. Yater, W. M.: Maintenance of the Functional Integrity of Occluded Large Arteries as Demonstrated by Thorotrast Arteriography, Am. J. M. Sc. **194**:372, 1937.

artery normally empties into the same vessel a short distance below its origin.

These observations are in essential agreement with those previously reported. They demonstrate again the value of arteriography in the study of the mechanism of the circulation in abnormal states and in individual instances in the decision on the prognosis and subsequent program of treatment.

Effects of Tobacco.—While tobacco smoking cannot be regarded as an etiologic factor in any of the diseases of the vascular system, there seems to be a definite tendency to believe that it plays an important part in vascular diseases of all types.

Chapman [18] has reviewed the experimental and known effects of tobacco on the vascular system. He states that there is sufficient information to prove that tobacco is definitely harmful to those who possess a vascular system which is unduly subject to vasoconstriction. This is true not only in thromboangiitis obliterans but in arteriosclerotic diseases as well.

The average percentages of nicotine range as follows: in pipe tobacco, from 1.45 to 2.84 per cent; in cigars, from 0.91 to 1.8 per cent, and in cigarets, from 1.06 to 3.11 per cent. Nicotine is considered the most important deleterious factor in tobacco. The absorption in the mouth during smoking is estimated to be 66 per cent, and if the smoke is inhaled, as much as 88 per cent of the nicotine is absorbed. There is no difference in the effect on the vascular system even though so-called denicotinized tobacco is used. The amounts of nicotine and of irritating by-products in tobacco are increased by the amount of moisture in the tobacco, the rapidity of smoking and the tightness of packing. The last third of a cigar or cigaret will produce 15 per cent more nicotine in the smoke than the first portions.

Minnhaar [19] has studied the effects of tobacco smoking experimentally and has carefully observed its clinical effects. His findings are in accord with those of previous observers. He states that the effect of smoking in cardiovascular disease varies with the constitution of the patient and with the local reaction of the arteries of the heart and of the lower extremities. He concludes that smoking has a definite harmful action on the cardiovascular apparatus.

Golston [20] emphasizes the functional effect on the arteries of the heart and of the peripheral circulation. He states that the continued

18. Chapman, D. G.: The Effects of Tobacco Smoking on the Vascular System, Virginia M. Monthly **64**:454, 1937.

19. Minnhaar, T. C.: Pathogenic Role of Tobacco Smoke in Cardiovascular Disease, Rev. méd. del Rosario **27**:706, 1937.

20. Golston, H.: The Tobacco Heart, Virginia M. Monthly **64**:319, 1937.

use of tobacco may cause the development of organic disease and that the vasoconstriction which results may be a contributing cause of death or impairment of tissue integrity.

Herrell [21] reports an interesting case in which there was marked idiosyncrasy to tobacco. This patient showed the usual effects of cigaret smoking on the vascular system to a marked degree. In fact, the vascular reactions were so pronounced that severe subjective symptoms resulted. The demonstrable effects were an acceleration of cardiac rate, a sharp rise in blood pressure and a lowering of the temperature of the skin to an unusual degree. Cutaneous tests for sensitiveness to tobacco were performed with negative results.

Nye,[22] who has made some observations on the frequency of vascular diseases among Australian aborigines, found few instances of disease of this type. He states that these natives smoke a great deal and use the strongest kind of trade tobacco. It is his opinion that tobacco plays only a small part in the development of arteriosclerosis or hypertension.

Thienes and Butt [23] have been of the opinion that much of the work incriminating tobacco and nicotine as causing degenerative vascular disease in experimental animals is highly uncritical and based on poorly controlled experiments. In the repetition of some of this work they were impressed with the degenerative changes they found in their control animals, which often showed more evidence of vascular disease than those exposed to chronic nicotine poisoning. They conclude only that the acute peripheral vasoconstriction associated with the smoking of tobacco may exaggerate the effect of degenerative vascular disease of the extremities.

THROMBOANGIITIS OBLITERANS

Goodman [24] has made further studies on the relation of typhus fever to thromboangiitis obliterans. In considering the etiology of this disease he believes that all the factors except infection have been eliminated. Studies of the epidemiology of typhus fever indicate that there is an unusual coincidence of the two conditions. These diseases have occurred in large numbers of persons in the same classes, and typhus fever is

21. Herrell, W. E.: Idiosyncrasy to Tobacco, Proc. Staff Meet., Mayo Clin. **13**:1, 1938.

22. Nye, L. J.: Blood Pressure in the Australian Aboriginal with a Consideration of Possible Aetiological Factors in Hyperpiesia and Its Relation to Civilization, M. J. Australia **2**:1000, 1937.

23. Thienes, C. H., and Butt, E. M.: Chronic Circulatory Effects of Tobacco and Nicotine, Am. J. M. Sc. **195**:522, 1938.

24. Goodman, C.: Thrombo-Angiitis Obliterans and Typhus: Evidence of Etiologic Relationship, Arch. Surg. **35**:1126 (Dec.) 1937.

disseminated in its endemic form throughout the world. He points out that typhus is primarily a disease of the blood stream, the organisms eventually becoming embedded in the endothelial cells of the blood vessels. There is a proliferative reaction of the endothelium followed by thrombosis and complete occlusion in some instances. Gangrene is commonly a complication of typhus, and many patients show symptoms similar to those of thromboangiitis obliterans, according to the writer. The basis of the similarity is in the epidemiologic and pathologic pictures of these two diseases, which he noted as early as 1916. He undertook cutaneous tests with a vaccine prepared from the rickettsial organisms in both conditions. These tests were carried out with controls The vaccine gave uniformly positive reactions in persons who had thromboangiitis obliterans or Brill's disease or who gave a history of typhus fever. The same tests employed on persons with gangrene from other causes, such as arteriosclerosis and diabetes, gave entirely negative reactions. These observations deserve further study.

Costantini, Liaras and Bourgeon,[25] in discussing the gangrene associated with typhus fever, state that they do not find the same similarity described by Goodman but that the gangrene of typhus is usually of the dry type, involving either an extensive portion of the skin or a portion of the extremities. It usually occurs in the lower extremity. Then the skin alone is involved; usually a dry black plaque is formed with clearcut borders. The plaque is cast off, and the resulting wound is rapidly recovered with skin. The nodule of Fränckel is the specific lesion. The site of predilection is along the vessels. If such a lesion causes obstruction to the flow of blood, tissue impairment will follow.

Weber [26] comments on the relative infrequency of familial cases of thromboangiitis obliterans as reported in the literature and describes typical examples of the disease in a father and son.

Several reports of the occurrence of cerebral involvement in the course of thromboangiitis obliterans have come to attention. Giampalmo [27] discusses this localization of the disease. Meszaros,[28] Uyama [29]

25. Costantini, M.; Liaras, and Bourgeon: Remarques sur les gangrènes du typhus exanthématique, Presse méd. **46**:75, 1938.

26. Weber, F. P.: Thrombo-Angiitis Obliterans in Father and Son, Lancet **2**:72, 1937.

27. Giampalmo, A.: Beitrag zur Endarteriitis obliterans des Gehirns, Deutsche Ztschr. f. Nervenh. **144**:166, 1937.

28. Meszaros, K.: Thrombo-Angiitis obliterans mit Veränderungen am Augenhintergrund, Deutsches Arch. f. klin. Med. **180**:526, 1937.

29. Uyama, Y.: Ueber das Vorkommen der sogenannten "Thrombo-Angiitis obliterans am Auge" unter Berücksichtigung anatomischer Untersuchungen. Arch. f. Ophth. **137**:438, 1937.

and others [30] describe cases in which there were alterations in the vessels of the brain and fundi. Hausner and Allen,[31] in a review of 500 cases, found clinical evidence of cerebral involvement in 3 per cent. They comment on the rapid disappearance and recurrence of the neurologic manifestation noted in several cases. Psychic symptoms, such as confusion and irrational behavior, occurred with the onset of hemiplegia. In 3 cases hemiplegia preceded the symptoms of involvement of the peripheral arteries by several years. They also state that a common complication is hemianopia. Anatomic studies were not made in any of these cases, but the symptoms occurred in cases which were typical examples of the disease and there was no other apparent etiologic factor. Reports of other types of visceral involvement have been made. They correspond with the reports of such cases made in previous years.

Tartakoff and Hazard [32] report a case in which there was a small growth in the spermatic cord; after surgical removal it showed the typical pathologic characteristics of thromboangiitis obliterans. There was no other localization of the disease.

Littauer and Wright [33] report an unusual case in which there were acute ulcerations on all four extremities which occurred simultaneously.

ARTERITIS

In a paper in which he discusses the general subject of arteritis, Karsner [34] draws attention to the need for correlation of the views on this type of arterial disease. He states that critical examination of several reports shows that what has been called periarteritis nodosa does not fit the known pathologic or clinical characteristics of this disease. In attempting to clarify the pathologic consideration of arterial inflammation, he proposes the division of these disorders into primary and secondary types. The secondary types of arteritis, he considers,

30. Meves, H.: Ueber cerebrale Beteiligung bei der Thrombo-Angiitis obliterans (von Winiwarter-Bürger'sche Krankheit), Nervenarzt **11**:127, 1938. Straussler, E.; Friedmann, R., and Scheinker, J.: Ueber die Endangiitis obliterans (von Winiwarter-Bürger'sche Krankheit) unter besonderer Berücksichtigung der Hirnveränderungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:155, 1937. Hadorn, W.: Ueber Endarteriitis obliterans der Organe, Deutsches Arch. f. klin. Med. **181**:18, 1937.

31. Hausner, E., and Allen, E. V.: Thrombo-Angiitis Obliterans of the Brain, Proc. Staff Meet., Mayo Clin. **12**:653, 1937.

32. Tartakoff, J., and Hazard, J. B.: Thrombo-Angiitis Obliterans of the Spermatic Cord, New England J. Med. **218**:173, 1938.

33. Littauer, D., and Wright, I. S.: Simultaneous Quadrilateral Acute Ulcerations in Thrombo-Angiitis Obliterans: Report of a Case, Am. Heart J. **14**:466, 1937.

34. Karsner, H. T.: Primary Inflammation of Arteries, Ann. Int. Med. **11**: 164, 1937.

are those which are associated with known infectious diseases or are the result of direct extension of inflammation from adjacent foci. In addition to these types he discusses the primary group, which he classifies pathologically into the acute degenerative, necrotizing, exudative, vegetative, proliferative and organizing varieties. In addition to these he recognizes a group of chronic disorders. Most of the examples of arteritis studied were not limited to one of these pathologic characteristics but often included two or more. The vascular phenomena of rheumatic fever are striking examples of this. The arterial inflammation seen in small vessels may be necrotizing or exudative; even proliferative and vegetative changes occur. Chronic arterial changes likewise occur in this condition. In periarteritis nodosa almost all the acute and chronic features of inflammation in the small vessels are present. Proliferative phenomena occur in ergotism. Syphilitic disease of the smaller arteries, he considers, is characteristically exudative and necrotizing. He classifies this as a secondary type of arteritis; this is true of the type seen in tuberculosis, typhus fever and undulant fever.

Horton and Magath [35] have made additional contributions to the knowledge of an interesting condition which has been previously reported from the Mayo Clinic and which has been termed arteritis of the temporal vessels. A total of 9 cases have been reported. The pathologic picture somewhat suggests that of periarteritis nodosa except for the absence of aneurysmal sacs. The disease is limited to the temporal vessels. The course in these 9 cases was from four to six months, and complete recovery occurred in each instance. The clinical features were of interest. Headache was an outstanding symptom, being more or less constant and often worse at night. Malaise, weakness, fever and night sweats were usual. These symptoms were often present two to six weeks prior to obvious involvement of the temporal arteries. Pain sometimes was intractable, and difficulty in chewing food was invariably present. Later the temporal arteries became tortuous, large and prominent. Along the course of the vessels reddish, raised nodules were visible and occasionally palpable. In some instances the temporal arteries seemed to become completely thrombosed. In 2 cases phlebitis of the retinal veins was present. It is also interesting to note that all the patients belonged in the older age group, being over 50 years old.

Perlow and Bloch [36] report an interesting case of poisoning with ergotamine tartrate, which was administered for the relief of the pruritus of Hodgkin's disease. As the pathogenesis of gangrene in ergot poison-

35. Horton, B. T., and Magath, T. B.: Arteritis of the Temporal Vessels: Report of Seven Cases, Proc. Staff Meet., Mayo Clin. **12**:548, 1937.

36. Perlow, S., and Bloch, L.: Impending Gangrene of the Feet Due to Ergotamine Tartrate, J. A. M. A. **109**:27 (July 3) 1937.

ing has been considered a primary vascular spasm followed by thrombosis due to stasis and injury of the intima, it was thought by the writers that treatment with papaverine hydrochloride should be effective in halting the progress of gangrene if used before organic vascular changes develop. The fact that this course of treatment was completely successful in preventing the development of gangrene is interesting in view of the mechanism of ergotism.

Puerperal gangrene resulting from the use of ergotamine tartrate is also reported by Benson.[37]

PERIARTERITIS NODOSA

Periarteritis nodosa seems to be attracting more attention. At least it seems to be more frequently reported, and the diagnosis is made during life with greater frequency. The cause of the disease is still unknown. Leishman [38] discusses the pathologic picture, and his description fits well the one generally accepted. In his experience the disease occurs most frequently in young males. The complaints are of muscle pain, fever, abdominal pain, edema and weakness. Leukocytosis is usual, and sometimes eosinophilia is present. Tachycardia is out of proportion to the height of the fever. Cutaneous nodules are evanescent, often disappearing within twenty-four hours. The most characteristic lesion is a small nodule fixed in the skin but moving with the deeper tissues. These nodules are painless and occasionally purpuric or vesicular.

Kernohan and Woltman [39] emphasize the prominence of neurologic symptoms. Involvement of the peripheral nerves, they say, is especially common. Involvement of the cranial nerves may lead to blindness, diplopia, facial paralysis, deafness and dysphagia. The central nervous system may likewise be involved even to the extent of hemiplegia, delirium or coma. The spinal fluid may be under increased pressure and show an increase in the number of cells and an increased total protein content. They report 5 cases in which the neurologic symptoms were outstanding. The pathologic picture is the same in the cerebral vessels as that which has been described elsewhere.

Karsner [34] points out that critical examination of several reports of the disease shows that what is called periarteritis nodosa does not fit the known clinical or pathologic characteristics of the disease. He has

37. Benson, W. T.: Puerperal Gangrene: Report of Seven Cases in Four of Which Ergotamine Tartrate Was Suspected as Being Part Cause, Tr. Edinburgh Obst. Soc., 1936-1937, p. 81; in Edinburgh M. J., August 1937.

38. Leishman, A. W. D.: The Clinical Diagnosis of Polyarteritis Nodosa, with Report of Four Recent Cases, Lancet **1**:803, 1937.

39. Kernohan, J. W., and Woltman, H. W.: Periarteritis Nodosa, Proc. Staff Meet., Mayo Clin. **12**:554, 1937.

found that necrosis and exudation are the most frequent types of pathologic change seen in the vessels. In typical cases the cells of the exudate include both polymorphonuclear and mononuclear eosinophils. These cells are not mentioned in many case reports, and their frequency seems to be questionable, but Karsner believes such local eosinophilia to be of great importance in establishing the diagnosis. This finding, together with the other features of the diseases, particularly the nodules emphasized by Klemperer, should make it possible to avoid the inclusion of a wide variety of arterial inflammatory conditions under the term periarteritis nodosa.

Brenner [40] also emphasizes the importance of the cerebral manifestations of the disease.

Sandler [41] reports a case in which there were uremia and sepsis, with miliary abscesses in the lungs and kidneys. An unusual symptom was the appearance of ulceration of the mucous membrane of the mouth. Heinrich [42] observed 1 patient in whom the condition lasted for fourteen years. Vining [43] describes an instance of the disease in which the diagnosis was made on the basis of the presence of cutaneous nodules. This patient apparently made a complete recovery.

ARTERIOSCLEROSIS

The relation of altered cholesterol metabolism and the etiology of arteriosclerosis is discussed in several papers.

Menne, Beeman and Labby [44] state that atheromatous lesions always contain cholesterol, whether in herbivorous or in omnivorous animals. The process in man is comparable with that seen in animals. Any condition which lowers metabolism in man or animals will result in abnormally increased amounts or altered states of cholesterol in the blood and will further its deposition. They believe this to be the essential factor in the production of arteriosclerosis. The disease does not develop in those conditions which tend to deplete the blood of cholesterol. This is demonstrated by the fact that in rabbits fed cholesterol under conditions of increased metabolism, induced by feeding thyroid, the disease fails to develop. These authors agree that the two essential factors in the pro-

40. Brenner, F.: Zur Kenntnis der Hirnveränderungen bei Periarteriitis nodosa, Frankfurt. Ztschr. f. Path. **51**:479, 1938.

41. Sandler, B. P.: Periarteritis Nodosa, Am. J. M. Sc. **195**:651, 1938.

42. Heinrich, A.: Bericht über einen 14 Jahre lang beobachteten Kranken mit Periarteriitis nodosa, Ztschr. f. klin. Med. **132**:577, 1937.

43. Vining, C. W.: A Case of Periarteritis Nodosa with Subcutaneous Lesions and Recovery, Arch. Dis. Childhood **13**:31, 1938.

44. Menne, F. R.; Beeman, J. A. P., and Labby, D. H.: Cholesterol-Induced Arteriosclerosis in Rabbits, with Variations Due to Altered Status of Thyroid, Arch. Path. **24**:612 (Nov.) 1937.

duction of atherosclerosis are hypercholesteremia and mechanical stress. Points of mechanical stress furnish the locations for the deposits of lipoid. Once the infiltration of the substance into the tissue spaces and the lymphatic chains of the vessel wall is begun, its accumulation there will serve to produce a vicious circle of destruction, absorption and defensive regeneration. This is in agreement with the conclusions of Leary. Handovsky [45] also agrees on the role of the thyroid gland.

Davis, Stern and Lesnick [46] studied the cholesterol and fatty acid content of the blood in a group of patients with angina pectoris of atherosclerotic origin. The average values were found to be definitely higher than in the normal persons studied. There were some individual variations, so that these findings were not always constant. Some of the patients with angina showed a normal cholesterol value, while some of the normal persons showed elevated values. However, in the majority of cases of atherosclerosis there was a definite increase in the cholesterol content of the blood.

Rich and Duff [47] found that experimental arteriolar lesions having the characteristics of the lesions of arteriolosclerosis and arteriolonecrosis in human beings occur in the tissues adjacent to the site of injection of tryptic enzymes such as pancreatic juice, commercial trypsin and papain. The process develops rapidly, and many lesions occur in as short a time as twenty-four hours. The arterioles show thickening of the wall and narrowing of the lumen when no vascular disease existed previously. They are unable to explain the mechanism of the pathologic change, but they suggest that it may result either from the direct action of the substances on the walls of the vessels or from the action of products of protein decomposition.

Hueck,[48] in discussing the subject of arteriosclerosis, points out that the term includes several distinct types of vascular disease which he thinks must be separated. He divides the condition into three types. The first he considers as a primary type, with uniform thickening of the wall and fibrous hyperplasia. His second type is characterized by nodular thickening, which he considers secondary to inflammatory disease, such as endarteritis, periarteritis and necrotic arteriolitis, or to granulomatous conditions such as syphilis or rheumatic fever. A similar

45. Handovsky, H.: Due rôle de la thyroïde et de la parathyroïde dans le développement de l'artériosclérose, Schweiz. med. Wchnschr. **68**:425, 1938.

46. Davis, D.; Stern, B., and Lesnick, G.: The Lipid and Cholesterol Content of the Blood of Patients with Angina Pectoris and Arteriosclerosis, Ann. Int. Med. **11**:354, 1937.

47. Rich, A. R., and Duff, G. L.: The Production of Hyaline Arteriosclerosis and Arteriolonecrosis by Means of Proteolytic Enzymes, Bull. Johns Hopkins Hosp. **61**:63, 1937.

48. Hueck, W.: Ueber Arteriosklerose, München. med. Wchnschr. **85**:1, 1938.

type of condition may follow toxic damage to the wall or necrosis of the media resulting from vasomotor disorders. The third type is characterized by marked thickening of the wall, with a coincidental nutritional defect, such as the secondary form of arteriosclerosis with preceding lipoid or hyaline degeneration followed by calcification.

As the result of his studies in arteriography, Veal [49] has extended his observations on the pathologic relation of intermittent claudication to the blood supply in arteriosclerosis. He describes the normal vascular pattern as demonstrated by arteriography, without essential variation from that recorded in the review of last year. He has found several patterns of arterial obliteration which vary widely in extent. The presence or absence of symptoms of obstruction depend on the extent of the pathologic process and the presence or absence of an adequate collateral circulation. There may be a marked degree of sclerosis involving the larger vessels; but if the occlusive process has been slow in development and the collateral circulation has kept pace with the occlusion, the circulation may be adequate, and no subjective symptoms will occur. He was able to divide the cases of intermittent claudication into three groups. In the first, consisting of 21 cases, there was complete obstruction at some point of one of the large arterial trunks. In the second group, consisting of 6 cases, there was definite, marked narrowing of the lower portion of the femoral or popliteal artery. The constriction was uniform in some, while in others there were large atheromatous plaques protruding into the lumen. The collateral circulation in these cases varied considerably, and in some instances the collateral vessels extended the whole length of the extremity. However, small branches to the muscles were few, although the blood supply was adequate to maintain the nutrition of the extremity. In the third group, consisting of 14 cases, the large vessels of the extremity were patent throughout their course, and their lumens were normal or nearly so. The defect in this group was in the small branches distributed into the muscles. They were few, irregularly placed and shorter than normal. There was marked diminution in the number of fine terminal branches. The obstruction in this group was in the small vessels supplying blood to the muscles, and it is presumed that the arterioles and capillaries were likewise involved. The single abnormality common to all three groups was the obstruction of the small branches to the muscles, with their fine terminal arteriolar and capillary arborization. This was the only abnormality noted in the third group, but it was also present in the first two.

As the result of treatment when improvement was taking place, further arteriographic studies showed no change in the large vessels, but

49. Veal, J. R.: The Pathological Basis for Intermittent Claudication in Arteriosclerosis, Am. Heart J. **14**:442, 1937.

an increase in the number and in the size of the terminal branches to the muscles was invariably noted. Cases have been described in which there was obstruction of the popliteal artery, with gangrene of the foot, and in which intermittent claudication was not present. In such instances the supply of the small branches to the muscles was adequate. Veal also comments on the fact that the integrity of the muscle cells in such conditions remains unimpaired because they receive sufficient nutrition by way of the tissue spaces from either the venous or the arterial side of the circulation. So it is only in instances of extreme involvement that necrosis of muscle tissue may be expected actually to occur.

Bernheim and London [50] comment on the similarity of the symptomatology in obliterating arteriosclerosis and in thromboangiitis obliterans. The decreased peripheral blood supply in both diseases is due in part to organic changes in the vessel walls which cause them to be obliterated or narrowed and in part to functional vasoconstriction. Vasospasm, they believe, is a factor of as much importance in arteriosclerosis as it is in thromboangiitis obliterans except in the advanced cases, in which the walls of the vessels are too rigid to respond. The vessels of the extremities are unduly sensitive to vasoconstricting influences, such as exposure to cold, the use of tobacco or a deficient diet. Vasoconstriction in such cases is prolonged beyond the normal response in more or less continuous vasospasm. They found an increase in the viscosity of the blood in arteriosclerosis as well as in thromboangiitis obliterans. The patients with arteriosclerosis respond as well or better to treatment than do those with thromboangiitis obliterans. Their methods will be discussed under the subject of therapy.

Veal,[51] in discussing the various factors in the mortality rate in cases of arteriosclerotic gangrene, points out the importance of considering this disease not from the standpoint of local peripheral involvement alone, but in view of the fact that it is a systemic disease, which implies generalized vascular deficiency. All the vessels of the body are likely to be involved, from the thoracic aorta to the terminal branches. In dealing with arteriosclerotic gangrene the effects of the disease on the heart, kidneys and other vital organs must be considered as well as the local complications of infection and gangrene. He states that the arteriosclerotic subject manifests the same susceptibility to infection as does the diabetic patient, although in a more sluggish manner. Infection is often deep seated and spreads along the tissue planes, possibly not

50. Bernheim, A. R., and London, I. M.: Arteriosclerosis and Thrombo-Angiitis Obliterans: Report of Cases and Treatment, J. A. M. A. **108**:2102 (June 19) 1937.

51. Veal, J. R.: Factors in the Mortality Rate of Arteriosclerotic Gangrene: A Comparative Study of Two Hundred and Fourteen Cases of Surgical Intervention, J. A. M. A. **110**:785 (March 12) 1938.

becoming manifest in a true line of demarcation. If infection is not actually present with gangrene, it is always potentially present. Infection increases gangrene, and gangrene increases infection exactly in the same manner as they do in the diabetic patient. However, the constitutional reaction in the arteriosclerotic patient may not be so marked as in the diabetic. The patient is often listless and drowsy and sometimes stuporous and may show mild senile dementia. He may refuse food and fluid and is often indifferent to his surroundings. Such general symptomatic factors are of the utmost importance when surgical treatment is being considered.

Instances of youthful development of arteriosclerosis have been occasionally reported. Such a case is reported by Thomasen,[52] who describes the condition in a child of 8 years.

CONGENITAL ARTERIOVENOUS COMMUNICATIONS

Seeger [53] has published an excellent paper in which all types of normal and abnormal arteriovenous communications are discussed and the literature is reviewed. The characteristic physiologic and pathologic aspects of normal arteriovenous anastomoses and abnormal arteriovenous fistulas are reviewed in detail. Much of this material has been considered in previous reviews.

In discussing arteriovenous fistula the essential characteristics are considered by the writer. They are sufficiently important to be repeated here. There is a high admixture of arterial and venous blood in the regional or deep veins of an extremity. The local effects are those manifested by the abnormalities of the vessels themselves. The vein below the point of the anastomosis is dilated by the increased volume of blood contained in it. This results in a pressure greater than that which the vein is capable of withstanding. As a result the vessel becomes dilated and tortuous. The larger the fistula and the longer its duration, the more widespread is the venous involvement. The involved artery shows a thinning of its walls. It becomes dilated, and degenerative changes in all its coats take place proximal to the fistula. This varies with the extent of the fistula.

The regional effects are the changes which occur in the limb affected. The first is hypertrophy, shown by an increase in the size of the extremity, not only in circumference but occasionally in length in the case of congenital communications. There is an increase in surface temperature, and trophic changes frequently occur. The latter are

52. Thomasen, E.: Arterienverkalkung bei einen 8-jährigen Knaben: Nach Behandlung mit Vitamin-D? Acta med. Scandinav. **95**:505, 1938.

53. Seeger, S. J.: Congenital Arteriovenous Anastomoses, Surgery **3**:264, 1938.

probably due to the diminution in the flow of blood through the capillaries because of the much greater volume of blood passing through the abnormal communication. The increased pressure in the veins impedes the return of deoxygenated blood from the capillaries. Consequently a state of anoxemia becomes chronic in the distal portion of the extremity. Bruits and thrills may be found. The general or symptomatic features of the condition depend on the disturbance in function of the circulatory system produced by the fistula. Because the fistula short circuits the blood away from the capillary system, a decrease of peripheral resistance results. As a consequence there is often a reduction in diastolic blood pressure with an increase in pulse pressure. The total volume of circulating blood is said to be increased. This is particularly true when there is a large fistula. Cardiac enlargement has been frequently noted, and sometimes symptoms and signs of cardiac failure have been recorded. This condition of the heart is not merely a coincident abnormality but is consequent on the fistula. The author quotes Leriche, who excised a large arteriovenous aneurysm from a patient who had cardiac decompensation and considerable cardiac enlargement. The heart returned to normal size, and signs of decompensation disappeared after the operation. The reason for the detrimental effect on the heart produced by the presence of abnormal arteriovenous communications is obscure. It seems reasonable to believe that there are three factors which may take part in this effect: One is the augmented filling of the right ventricle, dependent on the abnormal escape of blood directly into the veins. The left ventricle is called on to increase its output in order to maintain the general blood pressure. It is questionable whether this actually occurs. The total increased blood volume may be a still more important factor. Another interesting finding in cases of this kind is the slowing of the heart, which has been spoken of as Branham's phenomenon. In the cases which Seegar reports, infra-red photography proved to be an important aid in the differential diagnosis of hemihypertrophy. Arteriography was not of great help in his cases in locating the abnormality.

Horton and Baldes [54] have employed the electric stethophone with a recording device to differentiate the murmurs of peripheral aneurysm and arteriovenous fistula. The murmur of the former is typically systolic as to time, while the latter is characterized by a more nearly continuous murmur which has systolic accentuation. It is sometimes difficult to detect these differences with the unaided ear. A graphic record of the

54. Horton, B. T., and Baldes, E. J.: A Photographic Method of Recording Bruit: A Means of Differentiating Aneurysm and Arteriovenous Fistula; Preliminary Report, Proc. Staff Meet., Mayo Clin. **12**:823, 1937.

vibrations produced by such abnormalities serves to differentiate them not only as to differences in time with relation to the cardiac cycle but also as to recorded differences in vibratory rate.

GLOMUS TUMOR

Stabins, Thornton and Scott [55] have made some additional studies of this interesting condition. They point out particularly the derangement of the vasomotor mechanism, which is a typical feature of the disorder. The clinical pictures in the 2 cases reported are characteristic. There are mainly phenomena of vasodilatation. The vascular relaxation which occurs in these cases is probably the result of a reflex arc which extends at least back to the spinal cord or possibly to the sympathetic ganglions. The symptoms of vasodilatation endure for as long as eight weeks after operation for removal of the growth, as evidenced by the persistence of some discomfort in the region of the excised tumor. The phenomenon of pain observed in erythromelalgic states may have a similar reflex origin. The writers suggest that pain itself may be the efferent stimulus which produces the vasomotor response.

POPLITEAL ANEURYSM

Theis,[56] in reporting 5 cases of popliteal aneurysm emphasizes the consideration of this condition in all cases of unilateral peripheral circulatory disorder. This is true because the peripheral manifestations may occur before the onset of local symptoms in the popliteal space.

Arterial pressure is partially expended in dilating the aneurysmal sac. A reduction in pressure in the distal circulation occurs. The peripheral arterial pulsations and temperature are then reduced. With muscular activity or with vasoconstriction from exposure to cold, peripheral resistance increases. A still greater dilatation of the aneurysmal sac then results. Because of the location of the popliteal aneurysm deep in the popliteal space, early diagnosis on the basis of local findings is often difficult.

Theis has found that oscillometric curves show three distinctive features characteristic of the aneurysm: There is an increased height of the curve above the normal limits in the region of the disorder. There is absence of normal distal reduction in height from the thigh to the ankle. Finally, there is fluctuation in the height of the curve as the result of

55. Stabins, S. J.; Thornton, J. J., and Scott, W. J. M.: Changes in the Vasomotor Reaction Associated with Glomus Tumors, J. Clin. Investigation **16**: 685, 1937.

56. Theis, F. V.: Popliteal Aneurysms as a Cause of Peripheral Circulatory Disease, with Special Studies of Oscillomographs as an Aid to Diagnosis, Surgery **2**:327, 1937.

peripheral vasoconstriction or dilatation. Strenuous muscular exercise or vasoconstriction in the foot and leg as the result of exposure to cold was found to be associated with greatly increased oscillations in the aneurysmal sac.

EMBOLISM AND THROMBOSIS

Although the clinical features of these disorders are quite well known, several papers have appeared which correlate the findings and, as a result of increased experience, emphasize variations in the clinical features of these conditions.

Graham [57] discusses the etiology of arterial thrombosis and emphasizes the importance of the recognition of previous arterial and myocardial diseases with varying degrees of insufficiency of both the heart and the peripheral arteries. Damage to the lining of the vessels and slowing of the circulation as the result of myocardial impairment seem to be the most important etiologic factors of both disorders. Embolism is more frequent in the larger arteries than is thrombosis. There were 34 cases of embolism, with 14 cases of thrombosis.

Rykert and Graham [58] describe pain of two distinct types occurring in cases of arterial embolism. The first is that usually described. It is sudden and severe and is localized in the region of obstruction. This is followed by numbness and later by coldness. These later symptoms begin at the distal end of the extremity and extend upward to a point a little below the site of occlusion. After a time the original acute pain subsides and is often followed by severe pain in the area of numbness and coldness. Other signs of impaired arterial circulation are also present. These writers, in agreement with others, state that an embolus tends to lodge at a major bifurcation of one of the peripheral arteries. The lower extremities are involved more frequently than are the upper. In the leg the common femoral artery is most often occluded and in the arm the brachial artery. Both branches at the bifurcation may be occluded, or there may be complete occlusion of one and partial occlusion of the other. "A sudden development of numbness in one leg and tingling or numbness in the other point to embolism at the bifurcation of the aorta causing complete occlusion of the common iliac on one side and partial occlusion on the other." [57] If numbness is followed by tingling, this is an indication of a return of blood flow in the extremity. The pain with the occlusion of the aorta is usually referred to the back, whereas that of the iliac artery is referred to the abdomen. Occasionally embolism in this region may

57. Graham, D.: Embolism and Thrombosis of the Larger Arteries: Their Diagnosis and Treatment, Canad. M. A. J. **36**:33, 1937.

58. Rykert, H. E., and Graham, M. G.: Some Problems in the Diagnosis, Prognosis and Treatment of Acute Arterial Occlusion, Am. Heart J. **15**:395, 1938.

cause acute pain referred to the thigh, and occasionally acute pain develops in the lower part of an extremity after occlusion higher up. This may indicate that a fragment of an embolus has broken loose and secondary embolism has occurred in another distal location. The primary localization of an embolism is best determined by the location of the original acute pain or of the first bifurcation of the main artery above the upper limit of numbness and coldness.

In differentiating thrombosis from embolism Graham states that the clinical pictures of these two disorders are very similar. Thrombosis of a larger artery is not characterized by the sudden onset of pain, as is the case usually with embolism. A gradual rather than a sudden onset of numbness is characteristic of thrombosis. The presence of the etiologic factors necessary for the development of these conditions must always be considered. Thrombosis commonly results from infection, trauma, thromboangiitis obliterans or arteriosclerosis. In regard to the occurrence of pain as an initial symptom of embolism, Rykert and Graham found it present in 64 per cent, and in the later stages it was present in all their cases.

Pain is not always a prominent symptom. Numbness and tingling or motor paralysis may precede the pain by several hours. De Takáts [59] also points out in a recent paper, as he has before, that embolism may appear to be gradual in onset, with minor symptoms due to the appearance of small particles of a cardiac thrombus in an extremity before the main embolism occurs. Rykert and Graham state that when pain occurs at the onset and is referred to the level of the occlusion, this always precedes numbness and coldness. This pain is of short duration, lasting for only a few minutes, and is succeeded by prolonged distress or pain in a lower portion of the extremity in association with numbness and coldness. This temporary pain is not due to ischemia but is probably due to spasm at the site of the embolus, in their opinion. They believe that pain distal to the site of occlusion which develops later is due to ischemia. De Takáts shares this view. In some of his cases pain has been entirely absent. The absence of pain in acute embolism has been discussed by Allen. De Takáts states that thrombosis may occur so suddenly that it may be the initial symptom of widespread arterial disease. This may be the case in either arteriosclerosis or thromboangiitis obliterans. The infrequency of gangrene after an embolus has lodged in the upper extremity is also pointed out. The collateral circulation is usually adequate to maintain the tissue integrity. De Takáts finds thrombosis indistinguishable from embolism and states that multiple arterial thromboses, because of their multiplicity, may

59. de Takáts, G.: Vascular Accidents of the Extremities, J. A. M. A. **110**: 1075 (April 2) 1938.

simulate embolism. In discussing thrombosis and postoperative embolism, Bancroft and his associates state the belief that there must be some biochemical change in the blood which precedes or accompanies thrombophlebitis. While this is no doubt true in postoperative embolism, it is also probable that in peripheral embolism some similar alteration may occur. The factors favoring the production of thrombosis are still obscure.[60]

McKechnie and Allen [61] have studied the effect of the mechanical occlusion of individual arteries of an extremity. No pain was observed except that resulting from local pressure of the device used to obstruct the vessel. Arteries were occluded for as long as thirty minutes. The effect of such compression on the circulation of an extremity was not usually great. This is in sharp contrast to the results in cases of acute embolism. They agree that the pain which occurs in cases of embolism is due not to mere occlusion of a vessel but to the ischemia which results from a diffuse spasm involving the vessels of the extremity.

ANGIOSPASTIC DISTURBANCES

Of the group of vasospastic disorders, the most variable are those due to lesions of the central nervous system.

Pinkston and Rioch [62] report experimental studies on the ablation of cortical areas in the monkey. In general, their findings are in agreement with those of previous workers. The criterion for the determination of vasoconstriction was a decrease in the cutaneous temperature of the palms or of the soles. This decrease of cutaneous temperature was on the side opposite the lesions made in areas 4 and 6 (Brodmann) of the cerebral cortex. This decrease in temperature as compared with that of the opposite side persisted for as long as six months. They conclude that central mechanisms which control vasomotor reactions are localized in these areas. The mode of control and the pathways of conduction as well as the subcortical centers involved are obscure.

Allen and Craig [63] report an interesting case of tumor of the spinal cord in which the presenting symptoms and physical findings suggested impairment of arterial circulation of an organic type. They

60. Edwards, E. A.: Observations on Phlebitis, Am. Heart J. **14**:428, 1937.

61. McKechnie, R. E., and Allen, E. V.: Effect on the Circulation of Mechanical Occlusion of Individual Arteries of the Extremities: Relation to Arterial Embolism, Am. Heart J. **14**:127, 1927.

62. Pinkston, J. O., and Rioch, D. M.: The Influence of the Cerebral Cortex on Peripheral Circulation, Am. J. Physiol. **121**:49, 1938.

63. Allen, E. V., and Craig, W. M.: Vascular Clinics: III. Effect of Lesions of the Nervous System on Circulation; Report of a Case of Spinal Cord Tumor Which Produced Disturbances of Circulation, Proc. Staff Meet., Mayo Clin. **13**:131, 1938.

point out that a variety of neurologic lesions, varying from simple disuse of a member to hemiplegia and other central lesions, may produce rather striking peripheral vascular phenomena. Whenever the symptoms of suspected vascular disease are unusual or the findings on physical examination do not explain the symptoms adequately, a lesion of the central nervous system to which the disturbances of circulation are secondary may be suspected.

Heinbecker and Bishop [64] discuss the mechanism of the Raynaud syndrome under the title of spastic vascular disease. They do not subscribe to the view that this condition is the result of hyperfunction of the sympathetic nervous system. In fact, they point out that conditions in which hyperfunction does exist are not associated with the Raynaud syndrome. The fact that the paroxysm may be initiated by emotional excitement as well as by exposure to cold is easily explained by considering that the mechanism of constriction is a combined reflex and humeral one. Cold produces a reflex excitation of vasoconstrictor impulses to the blood vessels and also reflexly produces an increased secretion of epinephrine. Emotional activity is expressed through motor impulses over the sympathetic nervous system which affect blood vessels, sweat glands and the pilomotor mechanism and, in addition, produce increased secretion of epinephrine. They believe that reflex activity of the autonomic nervous system is a definite factor in the development of an attack. In normal persons on exposure to cold there is a reflex constriction of blood vessels. This is due not only to a primary local somatic reflex but in part to a generalized response characteristic of autonomic reflexes. They do not believe that this reflex response in persons with spastic vascular disease is any different from that in the normal person but that there is a definite quantitative increase in the response. They were able to induce the typical paroxysm by the subcutaneous injection of epinephrine hydrochloride or 10 to 15 units of insulin even in a warm room. Such an induced attack could be relieved by the administration of 20 per cent solution of dextrose intravenously. They explain that the same type of reaction occurs in patients with the Raynaud syndrome in response to the injection of epinephrine hydrochloride as to exposure to cold. This occurs in persons whose sympathetic nervous system is intact. This reaction to epinephrine is similar to the increased response in denervated vessels. The cause in their opinion is to be regarded as a constitutional change in the walls of the blood vessels which makes them respond more than normally to a normal vasoconstrictor impulse and to circulating epinephrine. Cold itself plays a minor role as a direct constrictor agent in the typical spasm. It is merely the stimulus.

64. Heinbecker, P., and Bishop, G. H.: The Mechanism of Spastic Vascular Disease and Its Treatment, Ann. Surg. **107**:270, 1938.

Several cases of spasm of the retinal artery [65] have been reported in association with the Raynaud syndrome. Such a case is that cited by Carpenter and Carpenter.[66] In spite of rather pronounced vasoconstriction, the retina showed no evidence of organic damage.

Under the term angiospastic claudication Pearl [67] reports a group of cases in which pain of the type characteristic of intermittent claudication was the outstanding symptom. He states that organic disease was excluded in the entire group. However, this condition may occur without any evidence of organic vascular disease or as an early manifestation of organic disease before obstruction has become sufficient to cause the condition. In this connection it is interesting to note that some of Veal's patients had an apparently intact arterial blood supply into the foot when the small vessels to the muscles could be shown by arteriography to be impaired.

Junghanns,[68] in discussing impairment of blood vessels due to the use of pneumatic tools, describes the usual picture but, in addition, states that in some cases the spasm may become so severe that death of local tissue may result. In 1 case there were pathologic signs with occlusion of small vessels somewhat similar to that seen in thromboangiitis obliterans.

De Takáts [69] again draws attention to a peculiar and poorly understood condition under the heading reflex dystrophy of the extremities. It has been described previously under a variety of names, such as post-traumatic osteoporosis, chronic traumatic edema, traumatic vasospasm, Sudeck's acute atrophy of bone and the like. The manifestations of this syndrome are rather diverse, and many of the preceding reports are based on a partial consideration of the condition. The vasomotor phenomena are often prominent at first but later may be overshadowed by the development of trophic symptoms. Hard, nonpitting edema is usually present but sometimes is not sufficiently outstanding to attract attention. Osteoporosis is usually present, and a picture of an irregular spotty atrophy of bone is shown roentgenographically. The condition resembles in some respects the atrophy of disuse. The edema is

65. Wauters, M.: L'artère rétinienne dans la maladie de Raynaud, Bull. Soc. belge d'opht., 1937, no. 74, p. 27.

66. Carpenter, W. M., and Carpenter, E. W.: Raynaud's Disease with Intermittent Spasm of the Retinal Artery and Veins: Follow-Up Report of a Case, Arch. Ophth. **19**:111 (Jan.) 1938.

67. Pearl, F. L.: Angiospastic Claudication, Am. J. M. Sc. **194**:505, 1937.

68. Junghanns, H.: Impairment of Blood Vessels by Continuous Concussions as a Result of Work with Pneumatic Tools, Arch. f. klin. Chir. **188**:466, 1937.

69. de Takáts, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937.

accompanied by pain, usually of paroxysmal type. The extremity is sensitive to changes in temperature and is particularly sensitive to superficial or deep pressure. There are no definite sensory changes, but ill defined hypesthesia may be present. The muscles are first hypertonic, owing to a reflex increase in irritability, but later become atonic. Early in the course of the disorder the temperature of the skin is higher than that of the normal side and later often lowered. Profuse sweating may occur. Trophic changes appear later. The nails become brittle and ridged. Eczema may occur, and herpetic lesions have been described. The skin may be glossy and bluish. The bone shows the characteristic spotty atrophy, which may become diffuse in the later stages. The capsules of the joints shrink. Movement of the affected joints becomes painful. Contractures may occur. Oscillometric studies show first an increase and later a decrease in the height of the curve. The hyperemic reaction to cold is delayed, and when it appears it endures much longer than normally.

This condition seems most frequently to follow mild trauma of various types, low grade infection, slight injury to a nerve, a burn or a frostbite. It probably occurs frequently but usually subsides before striking or intractable symptoms develop. In the rarer cases long-continued disability occurs and may even become complete. Pain has been so severe in cases of this type that amputation has been performed.

De Takáts states that in persons in whom the disorder occurs with maximum severity, constitutional inferiority is unmistakable. Emotional disturbances often aggravate the clinical symptoms. The disorder must be differentiated from functional neurologic states with atrophy from disuse. In addition the condition often resembles edema of venous or lymphatic origin, inflammatory conditions involving the bone or tendons, injuries and in the lower extremity spasmodic flatfoot.

The writer regards as the most important feature of this condition an exaggeration of a nutritional reflex, which is set up by the original injury or infection, which does not subside when the effect of the exciting cause disappears. It becomes a "fixed self perpetuating mechanism in which catabolic (destructive) activities are predominating."

This reflex is actuated by a chronic focus of irritability in the periphery. This produces a weak continuous stimulation through the ordinary sensory pathways to the cord, with relay to the lateral horn, and from here an efferent sympathetic impulse to the tissues follows. In 3 of the 5 cases reported by the author, all of the intractable type, this reflex was controlled by excision of the irritable focus. Sympathectomy completely relieved the condition in 1 case, and block of the sympathetic ganglions with procaine hydrochloride temporarily relieved the symptoms in another.

ACROCYANOSIS

After a study of a large number of cases of acrocyanosis, Stern[70] is of the opinion that this is a clinical disease entity the cause of which is frequent moderate cooling of the affected parts in conjunction with chilling of the body as a whole. Its mechanism is partial obstruction of the arterial blood supply of the skin of the hands and feet. He found no evidence of venous obstruction. In his opinion the site of the obstruction is in the arterioles of the skin and subcutaneous tissue. It is not merely arteriolar spasm, but there is actually an increase in the muscular tissue of these vessels. He states that there is no evidence of abnormality in the blood, central nervous system or glands of internal secretion. The successful treatment in such cases is continued warmth without exposure to cold for a period of months. These views are decidedly at variance with those of most observers.

A complete and careful study of a case of unusually severe acrocyanosis has been reported by Lambie and Morson.[71] In association with their study of this case they present a most exhaustive and careful discussion of the various manifestations of the symptom complex and the mechanism of the production of symptoms. Their patient showed the typical circulatory manifestations to a rather marked degree. She was a young woman of subnormal intelligence, so that she was unfit for any occupation. She was likewise physically defective, although no definite diagnosis of her condition was recorded. It seems that some endocrine disorder was at least a coincident if not an etiologic factor in the patient's condition. They found the vascular defect to be an obstruction in the smaller vessels in the hands and feet, either the arterioles, the arteriovenous anastomosis or the subpapillary arteriolar plexus. They thought all the vessels might be involved. In addition to the arteriolar constriction, capillary dilatation was found to be present. They believe that the capillary dilatation was probably dependent on the arteriolar constriction.

Their findings, in general, correspond well with the views of Lewis and Landis, as reported in a previous review. By means of nerve block with procaine hydrochloride they were able to obtain release of the arteriolar spasm, as were Lewis and Landis; but in their patient the change in color was observed before there was a rise of temperature in the surface structures. This is contrary to the findings on which Lewis and Landis based their conclusions.

No change in the temperature of the limbs followed the injection of acetylcholine. Injection of histamine phosphate intramuscularly was fol-

70. Stern, E. S.: Acrocyanosis, J. Ment. Sc. **83**:408, 1937.

71. Lambie, C. G., and Morson, S. M.: Acrocyanosis, M. J. Australia **2**:1070 1937.

lowed by flushing of the skin of the hands and feet without any rise in temperature. This reaction, they felt, was due to the general vasodilatation, which diverted much of the flow of blood to the deeper structures. When histamine was pricked into the skin of the affected area, no wheal was formed, but a more extensive flare appeared than in the normal skin. They interpret this as indicating that the arterioles reacted promptly and fully to histamine. Once they have relaxed, cyanosis disappears. There was no evidence of structural change in the arterioles. The fact that the flare was irregular and of greater extent than in the normal areas could be accounted for by the relaxed state of the capillaries and venules of the subpapillary plexus. The flare persisted for an unusually long period. This, they felt, was due to stasis in the capillaries. The local effect of epinephrine hydrochloride in blanching the skin illustrated normal ability of the arterioles and capillaries to contract. Solution of posterior pituitary, which acts almost exclusively on the capillaries in the human skin, produced a pale area of the same type as that seen in the normal subject. When it was injected intramuscularly, the type of reaction in the cutaneous vessels was normal except that the pallor in the hands was patchy and irregular. The writers have been unable to satisfy themselves as to whether or not the actual defect is local in the vessels or of central origin. They incline to the latter belief but can offer no direct evidence for its support. The fact that the vascular change is confined to the exposed parts, from which the loss of heat is greatest, especially the distal portion of the extremities, suggests that the defect lies in the central control of the vascular mechanism concerned with the regulation of body temperature or with the adaptation of vasomotor tone. The hypothesis of endocrine dysfunction as a cause of acrocyanosis did not appear to explain satisfactorily all the features presented in this case, although the clinical picture suggested in many respects that of Simmonds' pituitary cachexia. The authors point out that acrocyanosis may be confused easily with the Raynaud phenomena; in fact, they are inclined to believe that a number of cases reported in the literature should be classed in this group.

PHLEBITIS

Phlebitis is a type of vascular disease about which there has been considerable uncertainty. Edwards [60] has attempted to correlate information on this subject. He divides the cases into two major groups, those of suppurative and those of nonsuppurative or bland phlebitis. Suppurative phlebitis is seen in the immediate vicinity of a purulent focus. The involved vein may show no more clinical signs of inflammation than the nonsuppurative form. The clot is infected and undergoes purulent softening, and bacteria and portions of the clot may be dis-

seminated throughout the blood stream. Bacteria are invariably found in the involved portion of the vein and its contained clot. The nonsuppurative type of phlebitis is that usually seen postoperatively. This phlebitis also occurs in cases of fevers and of terminal states, as well as in cases of varicose veins. The involved vein shows the signs of inflammation often augmented by edema resulting from interference with the return circulation. The presence of bacteria in conditions of this kind is controversial. In many instances bacteria cannot be demonstrated, while in some instances infection no doubt is an important factor in producing the inflammatory process. It may be due to alteration in the character of the blood or to slowing of the blood stream. This is in distinct contrast to the definite findings in septic thrombophlebitis.

The histologic reaction consists of the so-called chronic inflammatory or reparative processes, with infiltration of lymphocytes and plasma cells. Polymorphonuclear leukocytes are uncommon. The infarct resulting from this type of phlebitis does not give rise to abscess formation. As a consequence of any type of phlebitis, irritation or stimulation of the sympathetic nerve fibers may take place. Whether by direct irritation or by reflex from the wall of the vein there is adequate stimulation for the production of vasospasm. This may take the form of vasoconstriction involving the vein itself or the adjacent small veins of the extremity or may induce a pilomotor reflex or even localized sweating.

More important than these reactions is the arterial constriction which may occur as the result of sympathetic irritation. This reaction may vary from a lowering of temperature, best accounted for by arteriolar constriction, to severe and complete spasm of a major artery of an extremity. The picture may closely resemble that of arterial embolism. The femoral vein is most frequently involved, and in this instance the condition is usually secondary to thrombophlebitis of the femoral or iliac vein. The condition may be ushered in by sudden severe pain along the course of the artery and later in the entire leg. Pulsation of the femoral artery is absent and the extremity cold and immobile. After a few hours the condition may disappear spontaneously, but actual thrombosis has been known to occur.[72] When the phlebitis has been previously noted, the condition is more readily recognized; but it often happens early in the course of venous involvement, so that the differential diagnosis is rendered difficult. Often the only indication of primary venous involvement is slight cyanosis above the area of ischemia and some dilatation of the surface veins. The number of such

72. Pringle, J. H.: Massive Ischaemic Gangrene with Thrombosis of Veins and Patent Arteries, Glasgow M. J. **129**:126, 1938.

cases reported has steadily increased.[73] The persistent disability after thrombophlebitis has been the subject of an investigation by Edwards and Edwards.[74] They have found that the inflammatory process involves the valves of the veins in various ways, so that the cusp is damaged or completely destroyed. The destruction of the valve or its damage results in insufficiency, so that the return flow of blood in the extremity is retarded. Even though the vein may be recanalized and the lumen adequately restored, the circulation becomes inadequate because of the incompetence of the valves in the vein or in the adjacent collateral channels. The valves in the collateral veins may be damaged, because these vessels become greatly dilated. The end result is permanent chronic impairment of the circulation in the extremity.

Edwards and Edwards[74] consider thrombosis of varicose veins to be due to factors other than infection, although they recognize the possibilities of latent infection. These factors are slowing of the blood stream, physical and chemical changes in the blood and alterations in the endothelial lining of the vessels.

The thrombotic process may begin spontaneously or follow some incident. It may vary from a chronic to an acute process and may be of long or short duration. It is often recurrent. It is most common in the superficial veins, through which it extends in both directions. Occasionally it remains localized but may extend to the deep veins of an extremity.

Pulmonary infarcts seldom occur from thrombosis in varicose veins if the patient is ambulatory, because with the impairment of the venous valves the hydrostatic pressure is sufficiently great to prevent escape of the clot through the saphenous vein; consequently it becomes more securely anchored in its original location. This is not true if the patient is confined to bed.

In addition to the usual factors which produce thrombosis, the possibility of alteration in the process of coagulation has been considered.[75] High clotting indexes were found in a number of cases. Prophylactic treatment instituted in a group of these was entirely successful, while in a control group the average number of accidents occurred. Heparin is a satisfactory prophylactic.[76]

73. Lindgren, S.: Arterien-Symptome bei den tiefen Beinthrombosen, Upsala läkaref. förh. **42**:415, 1937.

74. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, Surg., Gynec. & Obst. **65**:310, 1937.

75. Edwards, E. A.: Thrombophlebitis of Varicose Veins, Surg., Gynec. & Obst. **66**:236, 1938.

76. Bancroft, F. W.; Brown, M. S., and Chargaff, E.: Postoperative Thrombosis and Embolism, Ann. Surg. **106**:868, 1937.

PRIMARY VASCULAR HYPERTENSION

It is intended in this discussion not to review the subject of hypertension but merely to include briefly a few contributions concerned with the etiology of this important disorder. The hypertension of renal disease has been considered in a previous review.[77] It is obviously impossible in the light of present knowledge to separate essential hypertension from that of renal disease entirely.

Much of the present interest in this disorder has resulted from attempts to relieve its symptoms by means of operations on the sympathetic nervous system. This, in turn, has been the outgrowth of the surgical procedures applied to relieve the peripheral vasoconstrictor phenomena of Raynaud's disease and other vasospastic conditions.

The rationale of such a procedure is based on the assumption of the existence of increased tonus in the whole or in a part of the peripheral arteriolar system mediated by some central mechanism. That reflexes of peripheral origin or central impulses have an effect on blood pressure cannot be doubted, but that essential hypertension is of central nervous origin is exceedingly doubtful. Whether the essential cause is on this basis, that of impaired circulation of blood to the renal tissue or the result of an increased response to endocrine hormones, or a combination of these factors, still remains uncertain. Regardless of the obscurity of the cause, definite advances in understanding of this condition have been made, and it seems probable that the work of Goldblatt and his associates will prove to be the foundation on which the future knowledge of the subject will be based.

In a recent paper, which in part constitutes a review of this splendid work, Goldblatt[78] discusses the pathogenesis of experimental hypertension induced in animals by his method. He states that the results of experiments in which hypertension due to renal ischemia has been produced in dogs indicate that the mechanism of this type of hypertension is primarily a humoral mechanism of renal origin. These experiments indicate the importance of the reduced flow of blood to the functioning components of the kidneys as the primary cause of this type of hypertension and perhaps of the type of primary vascular hypertension observed in man which is associated with arteriolar disease of the kidneys. He suggests that the improvement which has been reported to result from operation on the sympathetic nervous system in many instances may be due to the improvement of circulation which is effected

77. McCann, S. W.: Bright's Disease: A Review of the Recent Literature, Arch. Int. Med. **61**:501 (March) 1938.

78. Goldblatt, H.: Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69, 1937.

through the kidney and not by a direct effect on the vasomotor mechanism of the splanchnic vessels. That the mechanism of experimental hypertension is humoral, involving a hypothetic substance of renal origin, is a theory based on only indirect evidence. Bilateral nephrectomy or complete occlusion of the renal arteries is not followed by hypertension. This is interpreted as being due to the absence of the hypothetic effective renal substance when the kidneys are absent. If circulation to the kidneys is completely shut off, the effective substance cannot enter the circulation. The cortex of the adrenal gland may play an important part in the development of this type of hypertension, while the medulla has no effect. Complete bilateral removal of the adrenal glands without substitution therapy has interfered with the development of this type of hypertension. The exact way in which the hormone of the adrenal cortex acts in conjunction with the hypothetic renal substance in the development and maintenance of hypertension has not been demonstrated.

The work of Goldblatt and his associates has definitely established that hypertension can be produced in experimental animals by the maintenance of renal ischemia. Hypertension of this type closely resembles the benign and malignant types seen in man. The severity of this hypertension and the coincident presence of impairment of renal function or its absence apparently depend on the degree of constriction of the renal arteries. The hypertension thus produced may be a general reflex arising from the kidneys or the result of some humoral substance elaborated by the kidneys. The evidence is preponderantly in favor of the latter view. It seems also to be true that the hormone of the adrenal cortex is in some way associated with the development of this type of hypertension. The work of Goldblatt has been confirmed by a number of investigators.

Harrison and his associates [79] have made some interesting observations on the effects of extracts of the kidneys of normal dogs and of dogs with hypertension induced by interference with the flow of blood through the renal arteries on the blood pressure of rats. They were able to demonstrate a rise in blood pressure in rats after the administration of saline extracts of the kidneys of normal dogs. Extracts of the kidneys of dogs in which hypertension had been induced caused a marked increase in blood pressure. There was a much greater pressor effect noted from the extract of one kidney in which ischemia had been produced in comparison with that of the other kidney of the same animal in which the renal circulation was normal.

79. Harrison, T. R.; Blalock, A.; Mason, M. F., and Williams, J. R., Jr.: Relation of the Kidneys to Blood Pressure: Effects of Extracts of the Kidneys of Normal Dogs and of Dogs with Renal Hypertension on the Blood Pressure of Rats, Arch. Int. Med. **60**:1058 (Dec.) 1937.

Williams, Harrison and Mason [80] have obtained two different pressor substances from the extracts of kidneys. One of their extracts contains a pressor principle, which can be separated from fresh saline extracts of renal cortical tissue. This is precipitated by ammonium sulfate. The properties of this substance are similar to those of Tigerstedt's renin. The other pressor principle is obtained from the acetone-insoluble fraction of renal extract. Whether these two are identical or not is not known. The authors do not believe that the pressor effect of fresh saline renal extract is due to tyramine or like substances.

The work of Freeman and Page [81] is of particular importance. They found that complete sympathectomy in dogs did not prevent the development of hypertension from compression of the renal arteries. They conclude that hypertension produced in this manner is not mediated through increased peripheral resistance due to reflex sympathetic vasomotor action. There is no increase in the total volume of blood plasma, and it is not the result of a reflex increase in cardiac activity. They believe that the physiologic factors which normally control the level of arterial blood pressure are not etiologically concerned in the development of hypertension induced by compression of the renal arteries in dogs.

Page and Sweet [82] have studied the effects of hypophysectomy on the arterial blood pressure of dogs with experimental hypertension. They found that when hypophysectomy was done on animals in which hypertension had been induced and maintained for several months, the blood pressure fell to levels slightly above normal within a period of twenty days. Hypophysectomy in normal dogs resulted in only a slight reduction of pressure. If the constriction of the renal arteries was increased after hypophysectomy there was again a rise in blood pressure which varied somewhat with the general condition of the animals. With administration of thyroid to such animals after the blood pressure had been reduced by hypophysectomy, the blood pressure was again raised moderately. The injection of estrogenic substance (estrone, or theelin) and gonadotropic substance from the urine of pregnant women (antuitrin S) had no effect. It seems possible, as they believe, that this effect is an indirect one. It may be due to the lack of secretions of the

80. Williams, J. R.; Harrison, T. R., and Mason, M. F.: Observations on Two Different Pressor Substances Obtained from Extracts of Renal Tissue, Am. J. M. Sc. **195**:339, 1938.

81. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery-Sympathectomized Dogs, Am. Heart J. **14**:405, 1937.

82. Page, I. H., and Sweet, J. E.: The Effect of Hypophysectomy on Arterial Blood Pressure of Dogs with Experimental Hypertension, Am. J. Physiol. **120**: 238, 1937.

adrenal and thyroid glands because of the absence of stimulation of these structures by the withdrawal of the hormones of the hypophysis.

Glenn and Lasker [83] performed total thyroidectomy on dogs both before and after the induction of hypertension by constriction of the renal arteries. There was no alteration in the production and maintenance of the elevated blood pressure in either group of animals.

It is interesting to note that Jores [84] has obtained substances from serum extracts of patients with hypertension which caused an increase in the size of the adrenal cortex of mice. This substance was found in 6 cases of essential hypertension but was not present in patients with eclampsia or toxemia of pregnancy.

Oppenheimer and Prinzmetal [85] studied the brachial-digital pressure gradient in normal and hypertensive subjects and in their patient with adrenal pheochromocytoma. The average pressure gradient for patients with hypertension was found to be approximately the same as that found in persons with normal or low blood pressure. In 3 cases of extreme hypertension there was a notable reduction. Only in the patient with chronic pheochromocytoma was the pressure gradient markedly increased, indicating constriction of arteries larger than the digital arteries. They conclude that in hypertension there is no increased resistance offered to the flow of blood by arteries as large as the digital. This is in agreement with the observation of Perlow,[86] who states that arterial spasticity is controlled by the autonomic nervous system and can be relieved by sympathetic ganglionectomy. Arteriolar spasticity, on the other hand, is controlled by some local nervous or chemical mechanism, the nature of which is unknown, and is not relieved by sympathetic ganglionectomy.

Arnott, Kellar and Matthew [87] have studied the hypertension that accompanies serum nephritis. They contend that the hypertension of acute diffuse renal disease depends on the integrity of the renal nerve supply and that it is probable that the mechanism is an autonomic vaso-

83. Glenn, F., and Lasker, E. P.: Effect of Total Thyroidectomy upon Production and Maintenance of Experimental Hypertension, Proc. Soc. Exper. Biol. & Med. **38**:158, 1938.

84. Jores, A.: The Role of the Hypophysis in High Blood Pressure, Especially in Essential Hypertension, Klin. Wchnschr. **15**:841, 1936.

85. Oppenheimer, E. T., and Prinzmetal, M.: Role of the Arteries in the Peripheral Resistance of Hypertension and Related States, Arch. Int. Med. **60**: 772 (Nov.) 1937.

86. Perlow, S.: Differentiation Between Peripheral Arterial and Arteriolar Spasticity in the Selection of Cases for Sympathetic Ganglionectomy, Surg., Gynec. & Obst. **64**:1015, 1937.

87. Arnott, W. M.; Kellar, R. J., and Matthew, G. D.: Hypertension Associated with Experimental Serum Nephritis, Edinburgh M. J. **44**:205, 1937.

constrictor reflex originating in the damaged kidneys. They doubt the possibility of a chemical mechanism which depends for its operation on the renal nerve supply.

Prohaska, Harms and Dragstedt [88] induced hypertension in normal dogs for periods as long as two weeks by the continuous intravenous injection of epinephrine hydrochloride. The amount necessary to maintain hypertension was sufficient to cause death from other systemic effects of this substance. They conclude that it does not seem probable that persistent hypertension in man can be due to hyperadrenalemia.

Binger and Craig [89] have reported an interesting case of sympathicoblastoma of the adrenal gland. The patient had persistent hypertension resembling the usual severe type of vascular hypertension without paroxysmal rises in pressure. Extensive sympathectomy was performed, with little fall in blood pressure. After exploration and removal of the tumor the blood pressure returned to normal and has remained so. It is interesting to note that this patient's basal metabolic rate was 61 per cent above normal.

Wolheim [90] has obtained from normal urine, urine from patients with chronic nephritis and urine of pregnant women a substance which is thermostable and has a definite depressor action. It was not obtainable from patients with hypertension. The intramuscular injection of this substance into patients with hypertension resulted in a definite fall in both systolic and diastolic pressure. The writer suggests that the absence of this substance may be responsible for hypertension.

Because of the conflicting findings reported after extensive sympathectomy, no attempt at this time will be made to discuss the physiologic influence of this operation.

Vaughan and Sullivan [91] discuss the possibility of an allergic factor in essential hypertension. They cite the case of a patient who exhibited allergic reactions to a number of foods. Dietary restrictions resulted in the disappearance of the high peaks of pressure. Both the systolic and the diastolic pressure failed to return entirely to normal. The pressure was further reduced by limitation of mental and physical activities. Two other patients with food allergy responded with a rise in

88. Prohaska, J. V.; Harms, H. P., and Dragstedt, L. R.: Epinephrine Hypertension, Ann. Surg. **106**:857, 1937.

89. Binger, M. W., and Craig, W. M.: An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, Proc. Staff Meet., Mayo Clin. **13**:17, 1938.

90. Wolheim, E.: A New Depressor Substance Elaborated by the Body and Its Meaning for Essential Hypertension, Acta med. Scandinav. **91**:1, 1937.

91. Vaughan, W. T., and Sullivan, C. J.: On the Possibility of an Allergic Factor in Essential Hypertension, J. Allergy **8**:573, 1937.

systolic and diastolic pressures after the ingestion of food to which they were known to be reactive. Liston [92] has had a similar experience. He reports sharp falls in blood pressure after the removal of foods from the dietary of persons who exhibited sensitization to them.

The susceptibility of the Negro to vascular disease has been spoken of for many years. Weiss and Prusmack [93] have made comparative studies in regard to essential hypertension in a large group of Negroes and white persons. The disease occurred a decade earlier in the Negro than in the white persons. Of the Negroes, 10.1 per cent were below the age of 40, while only 3.6 per cent of the whites showed the early appearance of hypertension. The sex distribution was about equal. One or more of the major complications of hypertension occurred in more than 75 per cent of the Negroes, in contrast to a 66 per cent occurrence in white persons. The mortality and morbidity of essential hypertension were found by Moritz and Oldt [94] to be greater in Negroes than in white persons. The average age at the time of death was likewise lower for the Negroes.

Guild, Kindell and Gibson [95] report 2 cases of extensive arteriolar sclerosis in 9 year old children with positive autopsy observations. In 1 case there was complicating pyelonephritis. There were extreme hypertension and marked cardiac hypertrophy in both but no evidence of myocardial failure. The presence of malignant hypertension so early in childhood is worthy of note. They have found in the literature reports of 20 other probable cases.

Moritz and Oldt [94] have made an important study of the occurrence of arteriolar sclerosis in hypertensive and nonhypertensive persons. They found that no type of chronic arteriolar disease was by itself pathognomonic of hypertension. Every type was found in persons known to have a normal blood pressure. The two most prominent and frequent types of arteriolar disease were found to be intimal hyalinization and intimal hyperplasia. Both are regarded as primary pathologic processes. The former is an aging phenomenon and is the counterpart in the arterioles of sclerosis in the arteries. The second may be the result of nonexudative, productive arteriolitis. They believe medial hypertrophy to be a secondary phenomenon due to distention of the vessels. Medial degeneration may be in part primary or perhaps asso-

92. Liston, O.: Hypertension Caused by Food Allergy, J. Missouri M. A. **34**:199, 1937.

93. Weiss, M. M., and Prusmack, J. J.: Essential Hypertension in the Negro, Am. J. M. Sc. **195**:510, 1938.

94. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679, 1937.

95. Guild, H. G.; Kindell, F. B., and Gibson, T.: Arteriosclerosis in Childhood, Bull. Johns Hopkins Hosp. **62**:159, 1938.

ciated with medial hypertrophy. While disease of the media may occur in persons without hypertension, severe types of medial disease were seen only in persons with chronic hypertension. Perhaps the most significant finding in the work of these observers is the fact that arteriolar disease of the kidneys was almost invariably associated with hypertension. It was present in 109 of the 200 cases studied, and 97 of these proved to be cases of chronic hypertension. The absence of arteriolar sclerosis in the kidneys, conversely, indicated the absence of hypertension. No comparable correlation was found with respect to any other organ or tissue. They conclude that the only significant site of arteriolar sclerosis concerned with the etiology of hypertension is in the kidneys. They have also observed that the most important factor determining the rate of progression of the disease, with early death from renal insufficiency, is dependent not on the degree of hypertension but on the progressive character of the renal arteriolar disease, with a more rapid rate of destruction of renal tissue. These observations can be correlated with those in experimental hypertension.

Rytand [96] has been able to produce hypertension in rats by partial occlusion of the aorta. This occurs only if there is living renal tissue distal to the occlusion. His findings in this respect are similar to those of Goldblatt. The mechanical obstruction due to stenosis of the aorta never resulted in hypertension when all the renal tissue was above the point of occlusion.

TREATMENT

During the past year few original ideas concerning the treatment of peripheral vascular disease have come to our attention. The majority of the published articles verify established methods or describe various modifications.

Silbert,[97] in a timely paper, discusses the evaluation of results in the treatment of peripheral vascular disease. He describes the improvement in circulation following occlusion of a major artery without any form of treatment. After occlusion occurs, collateral circulation develops quickly for about a year and continues to do so at a slower rate for at least two or three years longer. After this first period the circulation remains at a remarkably stationary level for an indefinite number of years, during which the collateral circulation is maintained. In patients with arteriosclerosis there follows a third period, in which the collateral circulation itself becomes involved in the arteriosclerotic process, and a progressive diminution of circulation results. In the

96. Rytand, D. A.: Pathogenesis of Arterial Hypertension in Coarctation of the Aorta, Proc. Soc. Exper. Biol. & Med. **38**:10, 1938.

97. Silbert, S.: Evaluation of Results in Treatment of Peripheral Circulatory Diseases, Am. Heart J. **15**:265, 1938.

first period, treatment may accelerate the development of the collateral circulation, but it will develop without it. It is obvious that one must know to what stage the disease process has developed in order to evaluate therapy properly.

Silbert also considers the role of tobacco in the evaluation of therapy. Because of its vasoconstricting effect, tobacco alone may produce marked circulatory insufficiency in cases of partial organic occlusion. Hence, cessation of the use of tobacco will, in a number of cases, produce spontaneous improvement. Environmental changes in temperature and in the emotional state of the patient will likewise influence the size of the peripheral vessels and must also be considered in the proper evaluation of treatment.

Bernheim and London [50] report gratifying results in the treatment of arteriosclerosis by following a regimen somewhat similar to that employed for thromboangiitis obliterans. It is their experience that vasospasm is an underlying process in both diseases. The rationale of their therapy was, therefore, to increase the blood supply to the extremity by, first, relieving the vasospasm and, second, by decreasing the viscosity of the blood. The latter results in an easier passage of blood through the narrow and rigid vessels. In order to relieve the vasospasm the use of tobacco was forbidden. Patients were warned against undue physical exertion, exposure to cold and emotional disturbances. A diet high in calcium and vitamins was prescribed because of its favorable influence on vasospasm. Sodium citrate, in doses of 250 cc. of a 2 per cent solution, was given intravenously to lessen the viscosity of the blood. After this regimen the authors observed improvement in 83.9 per cent of the 99 cases of arteriosclerosis. In 79.6 per cent of the 54 cases of thromboangiitis obliterans, improvement was also noted.

Sandstead and Beams [98] report the relief of pain of neurocirculatory origin in 13 diabetic patients by the oral administration of sodium chloride. In 10 cases the pain was of neuritic origin, and in 3 it was of arteriosclerotic origin. In the latter cases the histamine test was used as an index of circulatory improvement. The daily dosage was 0.25 to 0.5 Gm. per kilogram of body weight given at interrupted intervals of two to four weeks over periods ranging from one to twelve months.

Favorable results in the treatment of endarteritis obliterans and ulcers were obtained by Teitge [99] with estrogen. Mild circulatory distur-

98. Sandstead, H. R., and Beams, A. J.: Relief of Diabetic Pain of Neurocirculatory Origin by Oral Administration of Sodium Chloride, Arch. Int. Med. **61**:371 (March) 1938.

99. Teitge, H.: Die Behandlung der Endangiitis obliterans und des Ulcus cruris mit Sexualhormon, Med. Klin. **33**:1153, 1937.

bances, such as coldness and tingling of the fingers, responded readily. Patients with decubitus ulcers, Raynaud's disease or diabetic gangrene did not respond favorably. Since endocrine disturbances were more common in elderly patients of either sex, he found this form of therapy most favorable in this group.

Kling and Sashin [100] used histamine iontophoresis in a large group of cases of Raynaud's disease, acroparesthesia, angioneurotic edema and thromboangiitis obliterans. Relief from pain was obtained in 60 per cent of his cases. Solution of histamine prepared in a dilution of 1:2,000 was found to be most beneficial. He considers histamine superior to mecholyl (acetylbetamethylcholine chloride) because it has more effect on the arterioles and capillaries, with fewer systemic reactions. Murphy,[101] using mecholyl iontophoresis, noted definite improvement in 31 of his 33 cases of thrombophlebitis. Edema subsided, and the patient was able to be up and about without the aid of a supporting bandage.

Edwards,[60] in his observations on phlebitis, stresses the influence of this disturbance on the sympathetic fibers of the extremity involved and its resulting vasospasm. To combat this he found heat, foreign protein or typhoid vaccine given intravenously, most efficacious. He believes that prolonged rest in bed is unnecessary, since the fearful stagnation clot seldom adheres to the walls of the veins, regardless of rest. It is his practice to tie off the deep vein in all cases in which an embolus had been dislodged, in order to prevent recurrence. Müller [102] is also of the opinion that prolonged rest in bed is unnecessary and that the patient should be up, with a compression bandage on the involved extremity.

Numerous articles have been recently published concerning the therapeutic value of roentgen treatment of peripheral vascular disease. Cottenot [103] reports beneficial results in the treatment of endarteritis obliterans and vasomotor disturbances. He found it to be both safe and effective. Henschen and Becker,[104] reporting their results in acute,

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100. Kling, D. H., and Sashin, D.: Histamine Iontophoresis in Rheumatic Conditions and Deficiencies of Peripheral Circulation, Arch. Phys. Therapy **18**: 333, 1937.

101. Murphy, H. L.: The Treatment of Thrombophlebitis, Surg., Gynec. & Obst. **65**:100, 1937.

102. Müller, A.: Die Thrombophlebitis und ihre Behandlung mit komprimierendem Gehverband, Med. Klin. **33**:793, 1937.

103. Cottenot, P.: Zur Röntgenbehandlung der Endarteriitis obliterans, Strahlentherapie **56**:569, 1936.

104. Henschen, C., and Becker, F.: Röntgenbestrahlung der akuten, der subakuten und der chronischen Phlebitis und Thrombophlebitis, Schweiz. med. Wchnschr. **67**:438, 1937.

subacute and chronic phlebitis and thrombophlebitis, found that four to twelve radiation treatments effected the disappearance of phlebitic symptoms. Each irradiation consisted of 100 to 200 roentgens, and the more severe the inflammatory process, the weaker the dosage. He believes that irradiation produces a general action by increasing the bactericidal action of the blood and stimulating the reticuloendothelial system and the formation of antibodies. Locally it produces alkalosis, dilatation of the capillaries, an increase in the lymphatic circulation and a reduction of edema and pain. Friedländer and Sgalitzer [105] obtained good results in migratory phlebitis by irradiating the spleen. They gave six doses of 150 roentgens each, two of which were given anteriorly, two posteriorly and the remaining two from the left side. The rationale of this type of therapy depends on the effect of the rays on toxins present in the reticuloendothelial system of the spleen.

The center of interest in peripheral vascular disease during the past year has been intermittent venous occlusion. The preliminary reports by Collens and Wilensky were reviewed last year, the details of this type of therapy and a résumé of the results obtained in a small group of cases being given. Recently they [106] have reported their experience in 124 cases. In addition to the technic previously described, an attempt was made to alleviate vasospasm by raising the environmental temperature. This was accomplished by simultaneously heating the extremity with short wave irradiation or diathermy. Best results were obtained in cases of thromboangiitis obliterans and peripheral sclerosis in nondiabetic patients. In the former group ulcers or gangrene healed in 71 per cent of the cases, and rest pain was relieved within forty-eight hours in 85 per cent. In the latter group ulcers were healed in all cases and gangrene in 25 per cent of the cases. Complete relief from pain was obtained within forty-eight hours in 82 per cent, and in many the oscillometric readings increased. In cases of peripheral sclerosis with diabetes, relief from pain was noted in 60 per cent, and ulcers or gangrene healed in 62 per cent. In this group, amputation was required in 24 per cent of the cases while the patient was under treatment. All 7 patients with embolus and acute arterial thrombosis were relieved of pain, and 4 completely recovered. Seven patients with large chronic varicose ulcers responded favorably. The authors feel that this method is capable of "increasing vascular capacity as is evidenced by the following phenomena: relief of rest pain, increase in walking capacity,

105. Friedländer, E., and Sgalitzer, M.: Die Phlebitis migrans und ihre Behandlung, Med. Klin. **34**:223, 1938.

106. Collens, W. S., and Wilensky, N. D.: Intermittent Venous Occlusion in Treatment of Peripheral Vascular Disease, J. A. M. A. **109**:2125 (Dec. 25) 1937.

regeneration of tissues, improvement in the nutrition of nails, and the growth of hair over areas which had become denuded as the result of obliterative arterial disease."

Allen and McKechnie,[107] using a sphygmomanometric cuff above or below the knee, thus producing intermittent venous occlusion, were not able to produce any evidence of significant or consistent vasodilatation, as measured by the cutaneous temperature. Under basal conditions they studied a group of 19 patients with or without peripheral vascular disturbances. The fact that the final temperature of the skin in individual cases did not vary within a degree either above or below the original level was significant to them, in that vasodilatation did not take place. The Council on Physical Therapy,[108] however, in a preliminary report, states that tests indicate that both the cutaneous temperature and the oscillometric curves increase after the application of the Collens-Wilensky apparatus. It was also noted that during venous occlusion there was a filling and stretching of the venocapillary bed and during release reactive hyperemia took place which brought on vasodilatation. It was noted, however, that no provision is made in this type of treatment for emptying the vascular bed effectively, and for this reason a certain amount of continuous venous stasis exists. Kramer,[109] de Takáts, Hick and Coulter [110] are in agreement with this report. Kramer in a study of 30 cases confirms the work of Collens and Wilensky. In 66.6 per cent of the cases definite benefit was obtained. Cramps were relieved in 77.7 per cent, fatigue in 83.3 per cent and pain in only 56 per cent, a figure considerably below that given by Collens and Wilensky. Although Kramer was unable to make complete studies, he did find an average increase in cutaneous temperature of from 1 to 3 C., as well as an increase in the oscillometric readings.

De Takáts, Hick and Coulter [110] adopted a triphasic cycle, consisting of (1) elevation of the leg, (2) venous compression while the leg is still elevated and (3) lowering of the leg to a horizontal position, followed by release of the compression. Venous hyperemia was obtained by the use of an ordinary sphygmomanometer, the cuff of which was

107. Allen, E. V., and McKechnie, R. E.: Effect of Intermittent Venous Occlusion on the Circulation of the Extremities, J. Lab. & Clin. Med. **22**:1260, 1937.

108. Collens-Wilensky Intermittent Venous Occlusion Apparatus: Preliminary Report, report of Council on Physical Therapy, J. A. M. A. **109**:131 (July 10) 1937.

109. Kramer, D. W.: Periodic or Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, M. Rec. **147**:99, 1938.

110. de Takáts, G.; Hick, F. K., and Coulter, J. S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, J. A. M. A. **108**: 1951 (June 5) 1937.

8 inches (20 cm.) wide. They were able to show that intermittent venous hyperemia in a normal person increased the oscillometric readings during the venous constriction, with further increase immediately after release. The systolic and diastolic blood pressures during the period of constriction remained unchanged but decreased immediately after release of the constrictor. When vessel spasm was released either by placing the extremities under a heat cradle or by sympathectomy, the results were similar. Less striking findings were obtained in patients suffering from arterial disease. A rest period after compression was advocated in order to prevent a refractory stage. The passive elevation of the extremity allowed the venocapillary bed to empty sufficiently. The necessity for the two last-mentioned procedures was demonstrated by measuring the oxygen content and saturation of the blood from the femoral vein draining the treated extremity. Oxygen saturation was found to be fairly well maintained. These authors conclude that the mechanism involved is a mechanical filling and stretching of the vascular tree because of compression. After release a chemical vasodilatation takes place as a result of an oxygen debt, thus affecting the capillary pressure, the lymph flow and the saturation of the tissues and venous blood with oxygen.

The practical aspect of their study resulted in a simple, inexpensive method of producing intermittent venous hyperemia by utilizing the aforementioned triphasic cycle. A sphygmomanometer with an 8 inch cuff is inflated by the patient or an attendant. The amount of pressure varies between 60 and 90 mm. of mercury, never exceeding the diastolic pressure. In cases of edema, cyanosis, ulceration or gangrene, 40 mm. of mercury is considered maximum at the beginning. The duration of compression depends on the appearance of definite rubor, usually within one or two minutes. The duration of release always exceeds the period of compression, usually being twice as long. During the rest period, one minute is always allowed for elevation. Treatments are given twice daily for periods of thirty minutes. Ten cases of obliterative vascular disease were studied. Improvement in coldness and numbness was noted in 5 patients, 7 patients were able to walk farther before claudication developed and rest pain was relieved in 4 patients.

Recently, de Takáts [111] reported his observations on 50 patients who had had fifty treatments or more. He noted that coldness and numbness were the first symptoms to be relieved. Intermittent claudication improved slowly. Rest pain was the last to be relieved. This he explains by the fact that rest pain is a sign of serious circulatory damage

111. de Takáts, G.: Intermittent Venous Hyperemia for the Treatment of Peripheral Vascular Disease, Physiotherapy Rev. **18**:7, 1938.

and is found in persons with little ability to form a collateral circulation. Pure vasospastic circulatory disorders were not influenced. If the pressure in the cuff is lowered, this form of therapy can be used on patients with chronic edema, lymph stasis or chronic ulcerations. Phlebitis, lymphangitis and spreading infections are listed as contraindications to this form of therapy.

Confirmatory reports are also made by Brown and Arnott,[112] who limited their study to cases of obliterative vascular disease. Thirteen cases are reported, and good results were noted in all except 1 case. Nocturnal pain was invariably relieved, in some instances within a few hours after treatment was started. Intermittent claudication, present in 10 of the cases, was relieved in all except 2. Six of the patients had varying amounts of gangrene, and healing was promoted in all except 1. The same authors,[113] in a preliminary report, describe three new types of apparatus for use in the intermittent filling of the cuff. Two of these machines are electric air pumps, while the other is a water pump. Wilson and Ogston[114] describe clearly a novel apparatus for intermittent venous occlusion, utilizing water pressure and siphonage to obtain desired pressure and release in the cuff. Using this apparatus they obtained good results in 10 patients suffering from claudication and gangrene. In this series the rest period was lengthened to four minutes.

Articles continue to be published confirming, standardizing and modifying suction-pressure therapy in peripheral vascular disease. Veal[115] advocates the visualization of the peripheral vessels by means of thorium dioxide in order to prognosticate the possible value of this form of therapy. He noted that in patients with an extensive collateral circulation the best results were obtained. In patients with marked diminution of the vascular bed, improvement was only slight, while in those with high occlusion and extensive vascular damage no improvement was ever noted. A small group of patients are reported to substantiate his contentions. Studies on the oxygen saturation of venous blood from the popliteal and superficial veins showed that in the first group it increased after one hour of therapy, while in those with little collateral circulation the saturation remained unchanged.

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112. Brown, J. J. M., and Arnott, W. M.: Treatment of Obliterative Vascular Disease by Intermittent Venous Occlusion, Brit. M. J. **1**:616, 1938.

113. Brown, J. J. M., and Arnott, W. M.: Intermittent Venous Occlusion in the Treatment of Obliterative Vascular Disease, Brit. M. J. **1**:1106, 1937.

114. Wilson, C., and Ogston, A. G.: Treatment of Peripheral Vascular Disease by Intermittent Venous Occlusion, Lancet **1**:606, 1938.

115. Veal, J. R.: Alternate Suction and Pressure Therapy in Peripheral Obliterative Vascular Disease, Arch. Phys. Therapy **18**:640, 1937.

Krock [116] introduces a new, simplified suction-pressure machine of the light, compact, portable type in which the time ratio of suction to pressure can be changed to any desired amount. This machine is utilized particularly to obtain the ratio of one minute suction to one minute pressure, which has been found to be optimum, especially in cases of arteriosclerotic origin. He has noted that at the 1 : 1 ratio, anoxemia does not occur and in some instances the oxygen saturation of venous blood actually increases. He also reports a successful series of suction-pressure treatments of a patient with chronic obliterative arterial disease complicated by varicose veins. With the usual method, phlebitis readily developed, but after an elastic bandage was applied the treatments were carried out successfully. Yeager [117] believes that suction-pressure therapy is inadequate in thromboangiitis obliterans but beneficial in a large percentage of selected cases, particularly cases of arteriosclerotic peripheral vascular disturbances with fixed sclerosis of the arterioles. Leiner [118] reports his results obtained in 26 patients suffering from severe vascular damage. In the majority of the patients treated, relief from pain was obtained whether they were ambulatory or not. Trophic ulcers and gangrene improved. Becker [119] found this method of treatment satisfactory and advocates its use even though complications develop.

Eighty cases of occlusive arterial disease of various types in which suction-pressure therapy was used were studied by O'Neil.[120] The best results were obtained in cases of frozen feet and arteriosclerosis of diabetic origin. Good results were obtained in about half the cases of arteriosclerosis of nondiabetic origin, thromboangiitis obliterans and peripheral embolism. He emphasizes the fact that in peripheral occlusion due to emboli, good results cannot be expected from either embolectomy or suction-pressure if not carried out within four hours of the onset. It is his belief that suction-pressure therapy in the future will prove to be the procedure of choice. Rykert and Graham [58] are of a similar opinion, having had experience with both embolectomy and suction-pressure therapy. They believe that the final result of the treatment of embolic occlusion depends on the severity

116. Krock, F. H.: A Simplified Apparatus for Pressure-Suction Therapy of Obliterative Arterial Disease of the Extremities, South. M. J. **31**:294, 1938.

117. Yeager, G. H.: Passive Vascular Exercise in Peripheral Vascular Disease, Arch. Phys. Therapy **19**:158, 1938.

118. Leiner, G.: Die Saug-Druck-Behandlung der Erkrankungen der peripheren Gefässe, Klin. Wchnschr. **16**:783, 1937.

119. Becker, S.: Erfahrungen mit der "Saug-Druck"-Behandlung peripheren Durchblutungsstörungen, Med. Klin. **33**:1132, 1937.

120. O'Neil, E. E.: Suction-Pressure Therapy in Peripheral Vascular Disease, New England J. Med. **217**:828, 1937.

of the associated primary disease and that the results of suction-pressure therapy surpass those of embolectomy. They suggest that the ideal method of treatment for acute arterial occlusion is a combination of the nonoperative methods, namely, suction-pressure therapy, antispasmodic drugs and heat applied to the body.

SURGICAL TREATMENT: A CRITICAL REVIEW

By Dr. de Takáts and Dr. Beck

The surgical treatment of peripheral vascular disease is becoming more stabilized; new methods have not been described, but the more recent surgical procedures have been subjected to a closer scrutiny in regard to late results and the mechanism of their action. In this year's review we are including surgical procedures which are aimed at modifying the extracardiac part of the vascular tree and have not limited ourselves to operations on the vascular system of the extremity.

EMBOLECTOMY

Cornell [121] reviews the literature on embolism; he locates the site of obstruction by the point of maximum tenderness, which, however, in our experience is misleading. He stresses the fact that embolectomy should be performed within the first twelve hours. Of 20 reports of cases collected from the records of the New York Hospital, none records successful embolectomy. Rykert and Graham [58] report on a series of 36 patients from the Toronto General Hospital. The authors feel that in embolism of the large peripheral arteries, two distinct types of pain may arise. There is, at the onset of the attack, pain of short duration but of maximum severity which is probably due to arterial spasm at the level of the occlusion. This pain merges into and is replaced by late pain of ischemic causation, which arises distal to the occlusion. In arterial thrombosis the early pain is absent. Attention is called to the frequency of spontaneous recovery of the circulation in acute embolic occlusion of the upper extremity. The authors believe that the ideal method of treatment for acute arterial occlusions is a combination of the nonoperative methods, namely, suction and pressure therapy, antispasmodic drugs and heat to the body. They have performed embolectmoy in 11 cases, but their experience with this method has been unsatisfactory.

Lund [122] reports 55 cases of peripheral embolism. In the 30 cases in which the arteries were operated on, there were 27 embolectomies,

121. Cornell, N. W.: Arterial Embolism and Thrombosis, S. Clin. North America **18**:405, 1938.

122. Lund, C. C.: Treatment of Embolism of the Greater Arteries, Ann. Surg. **106**:880, 1937.

2 explorations and 1 ligation. Of the 27 patients on whom embolectomy was performed, 12 died in the hospital (44 per cent), 5 had amputations and 10 obtained successful results (37 per cent). Of 30 patients with embolism which was treated conservatively, 24 died in the hospital (85 per cent), 3 were discharged with good circulation (8 per cent) and 3 had amputations. The author believes that embolism of the upper extremities rarely leads to gangrene and that embolectomy is not needed. Results without embolectomy when the lower extremities are involved are poor.

Recently the impression has gained ground that early conservative measures make embolectomy unnecessary. The answer to this problem can be found by examining the fate of limbs after embolectomy and after conservative measures. Five patients who had survived acute vascular occlusion without gangrene and without embolectomy were studied.[59] In each case the extremity was pulseless and atrophic, the muscles were contracted and fibrosed and the skin was scaly and mottled. The legs were painful because of ischemic neuritis, and severe intermittent claudication was present. Such limbs cannot be compared with those from which a clot has been successfully extracted. For this reason we feel that in the small group of cases in which early conservative measures have not brought about an improvement in circulation but in which the limb is not yet ready for amputation, embolectomy should be attempted. Most frequently the groin and the popliteal fossa are explored, local anesthesia being induced. Clots in the aorta and in the common iliac artery may be approached from an incision in the groin and brought down by subperitoneal massage, as suggested by Nystrom.

PROXIMAL LIGATION OF THROMBOSED VEINS

In cases of deep thrombophlebitis of the lower extremities or pelvis in which fever persists for many weeks and months, the leukocyte count remains high and anemia develops or in which one or two showers of pulmonary embolism have occurred, ligation of the iliac vein above the thrombosis seems justifiable.[123] In weighing the results of such a ligation it must be remembered that the venous obstruction is already present and that the additional ligation will not add to the embarrassment of venous return if important tributaries are avoided. The drop in septic temperature and the cessation of further showers of pulmonary embolism were gratifying, according to both reports.[123]

123. Bancroft, F. W.: Proximal Ligation and Excision of Veins for Septic Phlebitis, Ann. Surg. **106**:308, 1937. Neuhof, H.: Excision of Vein for Suppurative Thrombophlebitis, ibid. **106**:311, 1937.

ARTERIOVENOUS ANEURYSM

An important contribution to this subject, which no one should miss who wishes to gain an insight into congenital and acquired communications between the arterial and the venous system, is the monograph by Holman.[124] This treatise is the result of painstaking experimental research and clinical observations which have been conducted for many years. The experimental arteriovenous fistula is described, with its physiologic effects on the heart, the blood pressure, the concentration of the blood and the total volume of blood. Clinical observations on acquired arteriovenous communications follow. There are chapters on intracranial, intrathoracic and mycotic arteriovenous fistulas and a description of congenital arteriovenous aneurysms. Of greatest interest to internists are the observations on ductus arteriosus and intracardiac fistulas, with some hopeful surgical implications. Interesting protocols are available in the appendix, and a complete bibliography is supplied.

The author assigns to the center of interest the variations of the total blood volume and its control in the body. He believes that valvular defects, abnormal congenital openings, aortic insufficiency, pulmonary insufficiency, a patent ductus and interventricular defects all produce a mechanical inefficiency which at their inception shows a lowered blood pressure which is corrected by an increase in blood volume. Future investigations, with perhaps improved methods, will have to confirm this interesting conception.

In a patient suffering from a pea-sized aneurysm of the circle of Willis, Dandy[125] placed a silver clip on the neck of the sac, which promptly collapsed, and then seared it with the electric cautery. All neurologic signs and symptoms, such as ptosis and shooting pain over the eye, disappeared. This is the first attempt to cure an aneurysm at that location by a direct attack. In the discussion of this paper, Rudolph Matas[126] gives a classic description of aneurysm of the circle of Willis, a small treatise in itself, to which we could not do justice in a short abstract. He points out that while extracranial ligation of the internal or common carotid artery remains the safest method of approach for all the aneurysms of the sellar, parasellar and infraclinoid carotid tract, no curative effect can be expected in the case of an aneurysm that rises from the branches of the circle of Willis except by a direct attack.

124. Holman, E.: Arteriovenous Aneurysm: Abnormal Communications Between the Arterial and Venous Circulations, New York, The Macmillan Company, 1937.

125. Dandy, W. E.: Intracranial Aneurysm of the Internal Carotid Artery, Ann. Surg. **107**:654, 1938.

126. Matas, R.: Aneurysms of the Circle of Willis, Ann. Surg. **107**:660, 1938.

SCALENOTOMY

The syndrome producing pain of ulnar distribution and vascular spasms, with radiation to the neck, shoulder and precordial region, is discussed by Spurling and Bradford.[127] In none of their cases was there any roentgenographic evidence of cervical rib. In 17 of 20 cases perfect relief was obtained by complete section of the anterior scalenus muscle. In 3 cases improvement but not complete cure was obtained. The authors believe that some cases of birth palsy without Horner's syndrome may be due to this mechanism. The scalenus syndrome may produce unilateral headache simulating migraine[128] or precordial pain simulating coronary disease.[129]

The incidence of cervical rib in 1,000 children under 13 years was 1.2 per cent.[130] In only 3 of the 12 children were there symptoms such as pain in the neck and arms, torticollis and atrophy of the extremity. Symptoms are not produced as a rule until ossification of the ribs takes place and until there is descent of the shoulder girdle.

SYMPATHECTOMY

The anatomic features of the sympathetic outflow to the extremities are still under debate. An important and timely contribution is that of Kuntz and his associates.[131] They point out that if preganglionic section, as advocated by Telford and by Smithwick and White (as cited in our last review), is carried out, important preganglionic connections between the cord and the inferior cervical ganglion are left intact, so that denervation is incomplete. They conclude that preganglionic components of the first thoracic nerve do play a significant part in the sympathetic innervation of both the sweat glands and the vascular musculature of the upper extremities. Thus complete sympathectomy of the arm cannot be accomplished by any operation which leaves the first thoracic nerve with its white ramus intact.

This study is an anatomic confirmation of our clinical experience that preganglionic sympathectomy is incomplete and that recurrences are not less frequent than after the postganglionic method.[132]

127. Spurling, R. G., and Bradford, F. K.: Scalenus Neurocirculatory Compression, Ann. Surg. **107**:708, 1938.

128. Kleinberg, S., and Levine, M. A.: Headache as Symptom of Cervical Rib, Ann. Surg. **105**:299, 1937.

129. Reid, W. D.: Pressure on the Brachial Plexus Causing Simulation of Coronary Disease, J. A. M. A. **110**:1724 (May 21) 1938.

130. Davis, D. B., and King, J. C.: Cervical Ribs in Early Life, Proc. Inst. Med. Chicago **12**:88, 1938.

131. Kuntz, A.; Alexander, W. F., and Furcolo, C. L.: Complete Sympathetic Denervation of the Upper Extremities, Ann. Surg. **107**:25, 1938.

132. de Takáts, G.: Analysis of End Results Following Sympathectomy for Peripheral Vascular Disease, Am. Heart J., to be published.

An important anatomic description of the "ascending pelvic colonic nerves" is given by Trumble.[133] In man the arrangement resembles that in herbivora. He believes that the description given by Telford and Stopford is inaccurate. For denervation of the lower extremity, the author simply cuts the chain at the upper border of the fourth lumbar vertebra and divides the gray ramus to the third lumbar nerve. He believes that the results are practically the same as those obtained by extensive ramisection with division of the trunk.

The effect of sympathectomy, previously studied in man, has been reinvestigated by the same methods in the dog by Freeman and Zeller.[134] After removal of the vasomotor control, the circulation seems to be dependent on the metabolic requirements of the tissues. This was found to be true in previous experiments on man, although the results were somewhat variable; in man the reflex secretion of epinephrine induced by unavoidable emotional disturbances could not be excluded. In order to eliminate the adrenal factor, the experiments were repeated on dogs in which one adrenal gland had been removed and the other denervated. It was found that the oxygen and carbon dioxide contents and the difference in p_H of the arterial and venous blood were constant in a single experiment over wide ranges of blood flow and metabolism. The volume flow of blood through the paw varied directly with the temperature of the bath in which the paw was immersed.

These findings add significant arguments for the hypothesis that the circulation after sympathectomy is controlled by the metabolic needs of the tissues but is no longer serving the purposes of heat regulation and is independent of external and internal stimuli that arrive to the vessels through the sympathetic fibers. As emphasized elsewhere, this is an important argument for sympathectomy in peripheral vascular disease.[135]

The blood flow before and after sympathectomy was measured in dogs with a Rein stromuhr by Schneider.[136] He found an increase of from 60 to 100 per cent immediately, several months, and as long as two years, after the operation. Arteries both to the skin and to the muscles showed an increase in flow. Stimuli from the carotid sinus

133. Trumble, H. C.: Strategic Points in the Lumbar and Sacral Outflows of the Autonomic Nervous System: Sympathetic Denervation of the Lower Limbs, M. J. Australia **2**:958, 1937.

134. Freeman, N. E., and Zeller, J. W.: The Effect of Temprature on the Volume Flow of Blood Through the Sympathectomized Paw of the Dog with Observations on the Oxygen Content and Capacity, the Carbon-Dioxide Content, and the p_H of the Arterial and Venous Blood, Am. J. Physiol. **120**:475, 1937.

135. de Takáts, G.: Sympathectomy in Peripheral Vascular Disease, Arch. Int. Med. **60**:990 (Dec.) 1937.

136. Schneider, D.: Experimentelle Untersuchungen zur lumbalen Sympathektomie, Beitr. z. klin. Chir. **167**:414, 1938.

were ineffective. He found not only constrictors but dilators in the sympathetic chain and believes that he obtained evidence of afferent sensory impulses by stimulating the central end of the trunk.

The sympathetic vasodilator fibers are discussed in a critical review by Burn,[137] who has contributed so much to the subject. He emphasizes the variations in different animals and feels that if knowledge of the sympathetic control of blood vessels had been based on the hare and not the cat, the current teaching might be different. In the muscles of the dog cholinergic vasodilators are readily demonstrable but not in the skin except that of the ear. In the rabbit and the monkey there are a few; in the dog and in the hare there are many. In man previous work of Lewis and Pickering demonstrated their presence.

This review, we believe, is an excellent argument against a blind application of cat physiology to conditions in man.

The overawed clinician has been put in his place so often by the experimentalist that his only answer to many problems is clinical research, with its well recognized limitations.

As a measure of sympathetic activity or paralysis, Richter and Levine [138] advocate the measurement of the resistance of the skin to the galvanic current. Cervicothoracic sympathectomy in 10 patients consistently produced a large increase in electrical resistance of the skin of the palms and less increase in the backs of the hands. Lumbar sympathectomy affected the same change in the dorsal and plantar surfaces of the foot.

We have found this method useful in detecting incomplete sympathectomy, in which a strip of skin of ulnar or femoral distribution remains moist or maintains its low resistance.

Surgical procedures on the sympathetic nervous system are for relief of symptoms rather than for eradication of diseased structures, as pointed out by Lehman.[139] Almost all diseases produce symptoms through the activity of the autonomic nervous system, such as fever and vomiting. In some diseases, however, symptoms of autonomic imbalance predominate, as in Raynaud's disease, and their symptomatic treatment by surgical means is warranted.

The argument as to whether preganglionic section is preferable to postganglionic sympathectomy still continues. J. C. White,[140] in his survey of surgery of the sympathetic nervous system, restates that pre-

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137. Burn, J. H.: Sympathetic Vasodilator Fibers, Physiol. Rev. **18**:137, 1938.

138. Richter, C. P., and Levine, M.: Sympathectomy in Man: Its Effect on the Electrical Resistance of the Skin, Arch. Neurol. & Psychiat. **38**:756 (Oct.) 1937.

139. Lehman, E. P.: The Surgery of the Sympathetic Nervous System, Surgery **2**:426, 1937.

140. White, J. C.: Progress in Surgery of the Autonomic Nervous System, New England J. Med. **217**:660, 1937.

ganglionic section for disorders of the upper extremities produces results which are comparable to the good results obtained by the customary lumbar sympathectomy for the lower extremities. After preganglionic section the vasoconstriction seen after the use of tobacco does not occur.

Telford [141] reports on twenty-five preganglionic sympathectomies and is satisfied with the results. He believes that the usual cervicothoracic sympathectomy should not be done; regeneration is avoided by implanting the sympathetic chain into the scalenus anticus muscle. Fibers from the first white communicating ramus are left intact, but they go chiefly to the head and can be ignored as far as the upper extremity is concerned. This is not in accord with the studies of Kuntz and his co-workers. Curiously, another study on Telford's material, published by Simmons and Sheehan,[142] presents the conclusion that a recurrence cannot be explained by Lewis' theory of the local fault in the vessel wall nor by the theory offered by White and Telford of sensitivity to epinephrine, which occurs a few days after operation, but that it is most probably due to an incomplete operation or to regeneration of fibers. They properly point out that the search for the cause of relapse of the Raynaud phenomenon following sympathectomy for the arm is one of the most important problems today in vascular surgery. Patients in whom block of the ulnar nerve fails to produce a rise in cutaneous temperature immediately after the operation may show such a rise later and have clinically a recurrence. The implantation of the cut end of the chain to prevent recurrence is reemphasized. Another group of patients show sweating immediately after the operation; this cannot be counted as a relapse but the result of an incomplete operation.

Observations in our clinic have prompted us to return to cervicothoracic ganglionectomy, although in a somewhat extended form, as after preganglionic section all the patients showed incomplete denervation and early clinical recurrence.

That regeneration is at least one definitely established reason for the recurrence of tonus is further corroborated by the excellent studies of Grimson, Wilson and Phemister,[143] who showed that after complete sympathectomy in the dog there occurred an initial drop in blood pressure, which returned to the preoperative level in about six months. They believe that during the period of lowered blood pressure the peripheral vascular tonus maintains the blood pressure but later there

141. Telford, E. D. S.: Sympathetic Denervation of the Upper Extremity, Lancet **1**:70, 1938.

142. Simmons, H. T., and Sheehan, D.: An Injury into "Relapse" Following Sympathectomy, Lancet **2**:788, 1937.

143. Grimson, K. S.; Wilson, H., and Phemister, D. B.: The Early and Remote Effects of Total and Partial Paravertebral Sympathectomy on Blood Pressure, Ann. Surg. **106**:801, 1937.

is a return of central control, even though this is not complete. When the central end of the sciatic nerve was stimulated or when the intracranial pressure was raised, the blood pressure rose; although a close study of the graphs indicates that the rise was incomplete. The authors suggest the possibility of the existence of vasomotor fibers in an extrasympathetic pathway.

SPLANCHNIC NERVE SECTION

The report cited in the preceding paragraph justly causes one to consider the effect of partial sympathectomy on hypertension in human beings. Page and Heuer [144] report 9 cases of transthoracic splanchnic section; 6 of the patients had severe essential hypertension and 3 malignant hypertension. Of the 6 patients suffering from essential hypertension, all had relief from subjective symptoms, but in 3 these returned within a year. The blood pressure fell in all cases but reached the preoperative level within six months. Urea clearance and concentration-dilution tests seemed unaffected by the operation. The pressor response to cold was not consistently altered. Papilledema disappeared in 3 cases but reappeared within a few months. The authors feel that this type of operation did not result in sufficient improvement to encourage further trial.

In previous years these authors advocated extensive section of the anterior roots, which they seem to feel offers better end results. To us, section of the anterior roots seems far too mutilating for the benefits obtained.

From the pioneer group of workers on the surgical treatment of hypertension comes a study of the physiologic effects of extensive sympathectomy for essential hypertension. Adson [145] has abandoned anterior root section and partial resection of the adrenal glands and now removes the splanchnic nerves, part of the celiac ganglion and the two lumbar sympathetic ganglions in two stages. Operation is advised if after the administration of sedatives or vasodilators a sizable reduction of blood pressure, especially that of the diastolic pressure, is obtained. An age of over 50, congestive heart failure, angina pectoris, marked renal damage and advanced arteriosclerosis are regarded as contraindications; but patients with retinitis, an inverted T wave, albuminuria and cerebral accident with recovery or slight reduction in renal function have not been excluded. They have had no death in 108 cases. In the favorable cases the operation resulted in reduction of blood pressure, reversion of the T wave, diminished libido and marked

144. Page, I. H., and Heuer, G. J.: Effect of Splanchnic Nerve Section on Patients Suffering from Hypertension, Am. J. M. Sc. **193**:820, 1937.

145. Allen, E. V., and Adson, A. W.: Physiological Effects of Extensive Sympathectomy for Essential Hypertension, Am. Heart J. **14**:415, 1937.

improvement with regard to headaches, nervousness and precordial pain. Of 44 patients who could be followed, 20 showed no reduction in blood pressure, 13 a fair result and 11 an excellent result. Many patients have had amelioration of symptoms without a reduction of blood pressure. Allen and Adson feel that their results have been sufficiently encouraging to warrant further trial of the method.

Obviously the selection of cases constitutes at present one of the most important problems in the surgical treatment of hypertension. Davis and Barker [146] accept only such patients with essential hypertension as have been proved to resist cyanate therapy, are young and are free from renal damage and whose blood pressure shows marked fluctuations. They report on 6 patients. The immediate fall in blood pressure was restored within ten days in all cases. However, 2 patients who showed no response to cyanate therapy have become responsive to the drug. The authors have no explanation for this effect.

Our observations on splanchnic section for essential hypertension have led us to conclude (1) that the distinction between essential extrarenal hypertension and renal hypertension is not easily made; (2) that the urea clearance is the most sensitive test of renal function, but even this test may fail in early renal damage; (3) that restoration of blood pressure occurred in all cases within a few weeks to a few months, and (4) that subjective improvement is marked and cannot be gaged by readings of blood pressure. At present we are studying the mechanism which is responsible for the restoration of blood pressure and are watching for changes other than those in the blood pressure following the operation.

ADRENAL DENERVATION

In previous years the literature contained several favorable reports dealing with adrenal denervation for the treatment of essential hypertension. An anatomic study of Hollinshead and Finkelstein [147] indicates that after resection of the lower thoracic and upper lumbar sympathetic chain in cats, regeneration of the nerves took place, with corresponding changes in the adrenal glands, within three months. The regenerated fibers arose from the ganglions and were unmyelinated. They believe that in larger animals sufficiently long segments might be removed to prevent regeneration and that the scar tissue so formed might provide an effective barrier.

A sustained hypertension was produced in dogs for periods up to two weeks by the continuous intravenous infusion of epinephrine

146. Davis, L., and Barker, M. H.: The Surgical Problem of Hypertension, Ann. Surg. **107**:899, 1938.

147. Hollinshead, W. H., and Finkelstein, H.: Regeneration of Nerves to the Adrenal Gland, J. Comp. Neurol. **67**:215, 1937.

hydrochloride by Dragstedt and his co-workers.[88] The amount required, however, was sufficient to cause death from the other systemic effects of the hormone, of which the inhibition of the motility of the gastrointestinal tract and the derangement of carbohydrate metabolism were probably the most important. For this reason it does not seem probable that persistent hypertension in man is due to hyperadrenalemia.

Rogoff and Marcus [148] have accumulated experimental evidence that the amount of epinephrine in circulation which is capable of causing sustained elevation of blood pressure would produce effects other than hypertension and would not be tolerated for more than a relatively short period. Besides, epinephrine disappears from the blood rapidly. They have also demonstrated that an increased concentration of epinephrine in the systemic circulation does not produce a detectable increase in epinephrine secretion from the adrenal glands. They deprecate the clinical practice of intervention on the adrenal glands as a treatment for hypertension.

In analyzing these experimental findings from the clinical standpoint, one must be impressed with the clearcut evidence that increased epinephrine secretion is not a cause of hypertension in human beings. This by no means excludes the possibility that certain substances which are produced in ischemic kidneys could not sensitize blood vessels to the action of epinephrine. In such a sense, then, the diminution in the output of epinephrine would still exert some influence on hypertension.

CELIAC GANGLIONECTOMY

Crile,[149] who has now performed a total of 391 operations on the sympatheticoadrenal system in 231 cases, first advocated adrenal excision, then adrenal denervation and later splanchnic section; finally, he has done 239 celiac ganglionectomies on 144 patients. The subjective symptoms, such as headaches, nervousness, dizziness, fatigue, palpitation and irritability, have been relieved over a period of a year in 78 per cent of the cases. Even though the blood pressure has not returned to normal in a number of cases, the subjective improvement has been marked. Moreover, these patients tend to become calmer and more equable in temperament, and the violent uprushes of blood pressure, with the disastrous results, which may accompany emotional outbursts may be mitigated.

Obviously this operation is just an extensive splanchnic nerve section with adrenal denervation. It more effectively prevents regeneration by eliminating a large group of cell stations in the celiac ganglions.

148. Rogoff, J. M., and Marcus, E.: Supposed Role of the Adrenals in Hypertension, J. A. M. A. **110**:2127 (June 25) 1938.

149. Crile, G.: The Clinical Results of Celiac Ganglionectomy in the Treatment of Essential Hypertension, Ann. Surg. **107**:909 (June) 1938.

That such patients become calm, are less excited, put on weight and have a definite change in personality has also been our impression of diabetic and hypertensive patients who have been subjected to splanchnic nerve section. As untoward effects on metabolism, intestinal motility and other functions are not observed, it seems to us that if any intervention on the sympathetic nervous system is considered at all, celiac ganglionectomy is the method of choice.

AMPUTATIONS

Arnell [150] reports on 117 patients with diabetic gangrene from the Maria Hospital in Stockholm seen between 1917 and 1934. There were 45 women to 72 men; 28 per cent were treated conservatively, 22 per cent had minor amputations and 50 per cent had major amputations. All major amputations were done above the knee. The total mortality was 27.4 per cent; for the amputations, 38 per cent. Causes of death in the order of their frequency were coronary thrombosis, sepsis, pulmonary embolism and pneumonia. Fifty per cent of all surviving patients were dead within a short time after dismissal from the institution.

Meleney [151] finds that hemolytic streptococci and staphylococci, and gas gangrene and tetanus organisms, as well as microaerophylic streptococci, are the organisms to be feared in amputations. If the gangrene is sharply demarcated, there is less danger of spreading infection than when there is much necrobiotic tissue in the process of breaking down. Material for culture should be taken from the muscles and the lymphatic system; if there is any doubt of infection, it is better to leave the stump open and treat it with a suspension of zinc peroxide.

Callander [152] reports on further experience with his method described in 1936.[153] In the 80 cases reported, the age in most of which was over 65, the mortality rate was 13 per cent, with only 1 case of postoperative gas gangrene.

Beverly Smith [154] states that the mortality in 50 amputations through the thigh for diabetic gangrene was 45 per cent. By the method suggested by him (which was described in a previous review [153]), it dropped

150. Arnell, O.: De la gangrene diabetique, Acta chir. Scandinav. **80**:464, 1937.

151. Meleney, F. L.: Bacteriology of Amputations, S. Clin. North America **18**:321, 1938.

152. Callander, C. L.: "Tendoplastic" Amputation Through the Femur at the Knee: Further Studies, J. A. M. A. **110**:113 (Jan. 8) 1938.

153. Scupham, G. W., and de Takáts, G.: Peripheral Vascular Diseases: Review of Some of the Recent Literature and Critical Review of Surgical Treatment, Arch. Int. Med. **58**:531 (Sept.) 1936.

154. Smith, B. C.: The Therapy of Surgical Complications of Diabetes Mellitus at Presbyterian Hospital in New York City, 1930-1935, Surgery **2**:509, 1937.

to 18.1 per cent in 20 cases. When the lesion was infected, sulfanilamide applied locally seemed helpful. In arteriosclerotic gangrene, Smith [155] again emphasizes the advantages of his plastic amputation through the lower portion of the leg, which facilitates the wearing of an artificial limb.

Silbert [156] treats all patients suffering from thromboangiitis obliterans with 5 per cent salt solution; ulcers are treated with cod liver oil. If marked pain is present and limited to the foot, crushing of the sensory nerves often gives relief for six months or a year. Up to 1925 at least one extremity was amputated in 60 per cent of the cases. Since 1925 only 6.4 per cent of 619 patients have required amputation, but only 2.7 per cent of those who truly cooperated have required amputation. The most important factor in obtaining results is complete abstinence from tobacco. If amputation is inevitable, an effort should be made to save the knee joint, as this will greatly facilitate the rehabilitation of the patient.

We have made considerable use of the Callander and the Smith type of amputation and believe that these methods deserve wider recognition. Both the preparation of the patient and the observation of technical details can reasonably reduce the mortality. The unavoidable mortality, due mainly to involvement of the cardiovascular apparatus, will always vitiate the late results.

155. Smith, B. C.: Amputation for Arteriosclerotic Gangrene, S. Clin. North America **18**:357, 1938.

156. Silbert, S.: Amputations in Thromboangiitis Obliterans, S. Clin. North America **18**:359, 1938.

News and Comment

American Board of Internal Medicine, Inc.—Written examinations for certification by the American Board of Internal Medicine will be held in various parts of the United States on Monday, Oct. 17, 1938, and on Monday, Feb. 20, 1939.

A formal application must be received by the secretary before September 15 for the October examination and on or before January 1 for the February examination.

Application forms may be obtained from Dr. William S. Middleton, secretary-treasurer, 1301 University Avenue, Madison, Wis.

Central Society for Clinical Research.—The eleventh annual meeting of the Central Society for Clinical Research will be held in Chicago, Nov. 4 and 5, 1938. The Drake Hotel will be the headquarters. Information regarding the meeting may be procured from the secretary-treasurer, Dr. Lawrence D. Thompson, 319 Chase Building, 4932 Maryland Avenue, St. Louis. The meetings will be open to the public.

Book Reviews

Les recto-colites ulcéreuses de cause inconnue. By Jean Coste, Ancien Externe des Hôpitaux de Paris. Price, 26 francs. Pp. 116. Paris: Gaston Doin & Cie, 1937.

This is a review of the subject of ulcerative colitis. The author groups the various ulcerative intestinal conditions other than tuberculosis and amebiasis under this general heading. The monograph is largely a review of the experiences of others, with the exception of a short final chapter on treatment with vitamin A. While the material constitutes an excellent review of the subject, the order of presentation is different from that usually employed in this country. The subject is handled as follows: The first chapter is on the history; the second is an introduction to the subject; the third is a clinical study, including a series of reports of cases; the fourth concerns the physical examination; the fifth, the clinical forms of the disease; the sixth, complications; the seventh, diagnosis; the eighth, pathologic anatomy; the ninth, etiology and pathogenesis, and the tenth, treatment.

In the chapter on the history of ulcerative colitis the author traces the origin of the disease to the report by Samuel Wilks in 1873 and then briefly reviews the work of Allchin (1885); Hale White (1888); Mayo-Robson (1893); Boas (1903); Lockhart-Mummery (1904); Hale White (1907-1909); Segond, Cade, Hutinel and Nobécourt (1912); Schmidt (1913), and Bensaude (1919). Under contemporary contributions he mentions especially the work of Bensaude and Antoine, of France, and emphasizes the authoritative studies of Schmidt, of Germany; Udaondo, of South America; Gallart-Mones, of Spain; Hurst, of England, and Bargen, of North America. He calls attention to the discussion of this disease given before the First International Congress in Brussels, in 1935.

In his introduction Coste stresses the importance of an accurate name for so-called ulcerative colitis. He states that in the absence of an accurate designation his study of the disease has been concerned largely with localization, definition of the clinical syndrome, prognosis and an attempt to give an exact description of the condition in the absence of a proved etiologic factor.

In his clinical study the author stresses the fact that ulcerative colitis is a form of dysentery with an insidious or abrupt onset. The important symptoms include painful, bloody evacuations, which frequently first are attributed to hemorrhoids. In the more severe forms fever is common. A large and interesting series of reports of cases is presented.

In the chapter on examination Coste stresses the importance of general physical, rectal and endoscopic examinations. He classifies the conditions into catarrhal, proliferating and intermediary types. The evaluation of the disease is presented graphically. He divides the clinical forms of the disease as follows: (I) according to evolution, into (1) very severe (often fatal), (2) of sudden onset, (3) chronic, (4) abortive and (5) only symptomatic, with subdivision of the symptomatic forms into (*a*) sanguinopurulent, (*b*) hemorrhagic and (*c*) purulent; (II) according to method of attack of the disease; (III) according to localization, into (1) local, which is subdivided into disease of (*a*) the rectosigmoid, (*b*) the cecum and ascending colon and (*c*) the transverse colon, and (2) diffuse, and (IV) according to age, into disease (1) of infants and (2) of persons in middle life.

In the chapter on complications the author reviews the experiences of others, mentioning particularly the detailed review of the cases reported from the Mayo Clinic. The chapter on diagnosis emphasizes the importance of examining the stools and of sigmoidoscopic and roentgenologic studies. Coste stresses the importance of differential diagnosis from neoplasms, polyps, diverticulitis, rectal gonorrhea, hemorrhoids, proctitis, amebiasis and bacillary dysentery.

Under pathologic anatomy an excellent description, as gained from the literature, is given. In the chapter on etiology and pathogenesis the author reviews, first, the reports on the relation of the organisms of bacillary dysentery to this disease and concludes that the evidence of their causal relation is not at hand. He discusses the hypothesis of a single etiologic factor, mentioning the work of Bargen; Gallert-Mones, of Spain, and Buttiaux and Sevin, of France, stressing that each confirms the other in part. He feels that a multiple bacterial etiologic factor should be considered.

The chapter on treatment is divided into five subheadings. Under the first is considered specific therapy. Administration of antidysentery serum is discussed as eliminative treatment. Coste stresses the fact that there is not enough evidence of a causal relation. He mentions the serums and vaccines prepared from the various forms of streptococci, stressing the use of the streptococcus vaccine advocated by Bargen and the polyvalent vaccine advocated by Surmont. The second subheading is concerned with symptomatic treatment, under which the author discusses intestinal lavage as indicated under special conditions, saying only that on occasions lavage will irritate and traumatize the intestine. He mentions the use of neoarsphenamine and of calcium and parathyroid extract, as advocated by Haskell and Cantarow. He suggests the employment of medicine for the production of shock, such as the antidysentery serum of Hurst, some vaccines and anaphylactic substances, such as those mentioned by Kalk. Under the third subheading he mentions the use of mineral waters. Material under the fourth subheading indicates that the aim of the surgical attack should be either diversion of the fecal current or resection of the intestine. Under the fifth subheading are discussed the author's studies and those of his colleagues on vitamin A therapy. He stresses the fact that the treatment is on a symptomatic and not an etiologic basis.

The monograph is well worth reading from the standpoint of a concise and rather critical review of this subject.

Gastroscopy. By Rudolf Schindler. Price, $7.50. Pp. 343, with 89 figures and 96 colored plates. Chicago: University of Chicago Press, 1937.

Schindler has met a pressing need for a book in English dealing with the subject of gastroscopy.

It is fitting that due credit should be given the author for his outstanding work in developing the present efficient flexible gastroscope and for his pioneer work in stimulating interest in this increasingly important diagnostic procedure.

The book reflects the enthusiasm of the author regarding the importance of gastroscopy in the diagnosis of gastric disease. The subject is presented in an interesting manner, and the book may be used not only as a guide to the neophyte in the field of gastroscopy but also as a source of stimulation to all those interested in the domain of gastroenterology.

The first portion of the book deals with the historical development of gastroscopy and the anatomic difficulties involved. This is followed by a painstaking description of the technic of the procedure. The main portion of the book is given over to a description of the gastroscopic appearance in the various forms of gastric disease and their treatment. This has been based primarily on the observations of the author, but careful reference is made to differences of opinion that exist among workers in this field.

One of the most interesting subjects dealt with is that of gastritis and its various subdivisions. Attention is correctly called to the fact that one of the greatest difficulties in dealing with the subject is to determine the limits of the changes that may occur in the normal gastric mucosa. There may be room for doubt in the author's statement that by means of gastroscopy one can absolutely determine the operability of carcinoma of the stomach and that exploratory laparotomy is not a justifiable procedure.

In the discussion of the relation of gastroscopy to other diagnostic procedures, one cannot help feeling that in his enthusiasm the author has not given other

procedures as much credit as they deserve. One might also question the wisdom and necessity of regarding gastroscopy as a routine diagnostic procedure, especially when the diagnosis has been established by other means.

Probably one of the most valuable and instructive parts of the book is the collection of beautiful colored drawings of the gastroscopic appearance in various diseases and conditions that may occur in the stomach.

The book, all in all, is very instructive and well presented and should be studied by all those interested in gastroscopy and the diagnosis of gastric disease.

The Harvey Lectures, Delivered Under the Auspices of the Harvey Society of New York, 1936-1937, Series 32. Price, $4. Pp. 245. Baltimore: Williams & Wilkins Company, 1937.

This last collection of lectures presented before the Harvey Society comprises eight essays, four of them bearing on important newer developments in the physiology of the nervous system. Wilder Penfield describes his electrical exploration of areas of the cerebral cortex of man and his first provocation of vocalization by this means and gives his views on epilepsy, dream states and automatism. An interesting conclusion is that all parts of the brain may be involved in normal conscious processes, but the indispensable substratum of consciousness lies outside the cerebral cortex, probably in the diencephalon.

The lecture of S. Walter Ranson deals with exploration of the hypothalamus, which led to the conclusion that this part of the brain, by way of the hypothalamico-hypophysial tract, controls the rate of elimination of water and that through its connection with the rest of the brain and spinal cord the hypothalamus activates the sympathetic system and also, though less directly, the somatic motor centers. Its stimulation or release from cortical control provokes the picture of emotional excitement and, conversely, its suppression is followed by emotional stolidity.

The lecture of Herbert S. Gasser is concerned with action currents in the nerves and excitation in the nervous system. Sir Henry Dale describes the part played by acetylcholine in the transmission of nervous effects through the ganglionic synapses, with particular reference to the objections encountered and the explanations for many of these.

Other lectures in the book are as follows: "The Passage of Fluid Through the Capillary Wall" by Eugene M. Landis; "The Investigation of Intermediary Metabolism with the Aid of Heavy Hydrogen" by Rudolf Schoenheimer; "The Scientific Work of the Health Organization of the League of Nations" by Thorvald Madsen, director of the Serum Institute, Copenhagen, and "The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes" by C. N. H. Long.

Many of these essays sooner or later probably will be regarded as classics, and physicians will be well repaid for time spent on their careful perusal.

Not So Long Ago: A Chronicle of Medicine and Doctors in Colonial Philadelphia. By Cecil K. Drinker, M.D. Price, $3.50. Pp. 183, with 20 illustrations. New York: Oxford University Press, 1937.

The native Bostonian is generally supposed to be a provincial person with a time-honored prejudice in favor of old things that have been established for a good many years and that do not change too rapidly—things like Harvard College, the symphony concerts or the Lowell Lectures. The native Philadelphian almost always can understand the Bostonian point of view, for he too has an inherited prejudice toward old things and likes to recall the days when persons of gentle birth realized the responsibilities entailed in being known as ladies and gentlemen.

"Not So Long Ago" is a charming book. It has about it the flavor of old Madeira and will appeal to any one with a nice palate, particularly any one entertained by the foibles of the dyed-in-the-wool Bostonian or Philadelphian.

Mrs. Elizabeth Drinker was a great lady of Philadelphia. She became associated through marriage with the Drinkers of Beverly who moved to Philadelphia before Philadelphia was there. It is her diary that has been edited by her great,

great grandson, who, by the grace of God, has returned to New England from Philadelphia and has lately presented excerpts from her diary to Boston as the basis of his series of Lowell Lectures.

The diary was written through the eventful years between 1758 and 1807. The editor has placed especial emphasis on what Mrs. Drinker observed of medicine, doctors and hygiene. She knew a good deal of obstetrics; she was familiar with tuberculosis, typhoid, smallpox and yellow fever; she served tea to Dr. Rush in the "parlor" and found his conversation agreeable, and she commented shrewdly on the peculiarities of other medical men, like Dr. Physick, Dr. Kuhn and Dr. Redman. The editor has been skilful in making Mrs. Drinker a thoroughly lively lady. He has selected interesting illustrations with which to embellish her diary. Her views on life in general seem close at hand. At the end of 1781, at the beginning of the "First New Deal," she wrote, "'Tis a bad Gouvernment under which we are liable to have our Houses seachd and every thing laid open to ignorant fellow prehaps thieves." To many of her readers those days will indeed seem not so long ago.

The Technic of Local Anesthesia. By Arthur E. Hertzler. Sixth edition. Price, $5. Pp. 284, with 142 illustrations. St. Louis: C. V. Mosby Company, 1937.

The sixth edition of this work includes a consideration of the few good anesthetics that are available for local anesthesia, the dosages and the methods of use, the combination of epinephrine with local anesthetics and the combination of local and general anesthesia. There is a description of the syringes and needles recommended for this work and of various other apparatus which is conveniently employed. The various blocks are described on an anatomic basis, as, for example, in chapter 4, local anesthesia for operations on the scalp, the cranium and its contents, and in chapter 5, local anesthesia for operations on the face, jaw and tongue. In the following chapters local anesthesia is described with respect to operations on the ear and mastoid cells, operations for trifacial neuralgia and operations on the fifth cranial nerve, cervical lymph nodes, buccal soft parts, thyroid gland, tonsils, larynx, trachea, mammary gland, thorax, lungs, spinal column and abdomen. Paravertebral and splanchnic anesthesia are dealt with in a chapter, as well as sacral and transsacral block anesthesia. There is a special chapter on spinal anesthesia, written by Dr. Irene A. Koeneke, this subject being considered in considerable detail. There are further chapters on local anesthesia for operations for inguinal and femoral hernias and also for umbilical and scar hernias and hernia of the linea alba and for operations on the penis, scrotum, urethra, bladder, prostate gland, female organs, rectum and upper and lower extremities. There is a short chapter on the intravenous use of sodium amytal, which has not been employed much clinically as a surgical anesthetic since 1930. The subject of preliminary medication is discussed briefly. This is a very useful book for the general surgeon because the author's preference is infiltration of tissue to be incised, which is the most effective method for use by the general surgeon unless he has been trained also in the methods of obtaining regional anesthesia. There are one hundred and forty-two excellent illustrations.

Practical Talks on Kidney Disease. By Edward Weiss, M.D., Professor of Clinical Medicine, Temple University School of Medicine. Price, $3. Pp. 176, with 10 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

This is an unpretentious, friendly little book that is well worth knowing. The author says that he had an attack of glomerular nephritis during his internship and ever since has been especially interested in renal disease. Evidently, too, he has also been interested in physicians. He has put together this volume "to assist the physician who practices general medicine to understand what is generally regarded as a difficult and confused subject."

The plan of the book is sensible. Renal physiology and tests of renal function are first discussed, next the signs and symptoms of renal disease are considered

and finally the various major forms of Bright's disease are elaborated on under the chapter headings glomerulonephritis, nephrosis, pregnancy and kidney disease and nephrosclerosis.

The author knows of what he writes and is familiar with the literature. His style is clear; he drives home simple truths, for instance, that nowadays the general practitioner must not be afraid of the ophthalmoscope. He paints a clear picture of what is generally believed regarding renal disease and its treatment and remains properly skeptical about the newer therapeutic procedures that are still under fire, such as the use of acacia in the management of edema or various operations on the sympathetic nervous system to cure hypertension.

The title of the book is a good description of its contents. Certainly here is a series of exceptionally practical talks on the modern problems of renal disease which many physicians, both old and new, will enjoy.

The Postmortem Examination. By Sidney Farber, M.D., Associate in Pathology, Harvard Medical School. Price, $3.50. Pp. 201, with 33 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

Nowadays, with the problem of adequate postgraduate medical education looming large on the horizon and with meticulous clinicopathologic correlation becoming increasingly important to clinicians and pathologists in medical schools, teaching hospitals and the better administered smaller hospitals, it is timely to have published a book dealing with the postmortem examination.

This new handbook is an excellent one, well constructed, well written, well illustrated and informative from beginning to end. There is a nice historical introduction to please the historical minded, and, better still, at the end is reprinted a protocol by Virchow which is a model of gross pathologic description. The bulk of the volume discusses pathologic technic in simple and clear terms, explaining the various procedures to be employed in a properly conducted necropsy.

There are twelve chapters in the book, and at the end of each is a short list of references to supplementary matter which should appeal to students. Finally there are given tables of average weights of organs compiled from various authoritative sources and a copy of the report of the New York committee on rules governing pathologists and undertakers. The latter is a useful document, which was included in the hope that it might "serve as a guide for similar committees in other cities of the United States."

On the whole, Virchow, Chiari, Warthin and Mallory and Wright should graciously welcome this newcomer; it will prove a respectable member of the Society of Good Books and, before long, much thumbed in all medical and hospital libraries, will occupy an honorable position on the same shelf with these distinguished predecessors.

Physical Diagnosis. By Don C. Sutton, M.D. Price, $5. Pp. 495, with 298 illustrations and 8 colored plates. St. Louis: C. V. Mosby Company, 1937.

So many excellent books on physical diagnosis have appeared recently, especially that of Major, in addition to the innumerable old standbys, that one wonders whether this new volume displays any original features. Perhaps the outstanding part is the illustrations, which are unusually good and are well selected to illustrate problems of physical diagnosis. The reviewer hesitates to say, however, that this new book is either better or worse than most of its predecessors.

Erforschung und Praxis der Wärmebehandlung in der Medizin einschliesslich Diathermie und Kurzwellentherapie. Edited by B. Rajewsky, M.D., and H. Lampert, M.D. Price, 9.50 marks. Pp. 185, with 82 illustrations. Dresden: Theodor Steinkopff, 1937.

Twelve papers which were read before the second conference on medical science at Frankfort, Germany, on the present status of heat therapy are included in this volume, together with a great deal of the discussion relative to them. The

papers deal with the practical or therapeutic use of heat, physiologic principles and the physical nature of the instruments used and the energy emitted by them. The last five papers will be of interest to various specialists, as they deal with the use of heat treatment in internal medicine, pediatrics, surgery, gynecology and balneology. The practitioner of physical therapy who is interested in knowing what he is doing when he uses heat will obtain much valuable information from a study of these articles.

Differentialdiagnose in der inneren Medizin. III: By Prof. Dr. Med. O. Naegeli. Price, 10.80 marks. Pp. 415 to 772, with 59 illustrations. Leipzig: Georg Thieme, 1937.

This volume is the third instalment of Naegeli's work on differential diagnosis. The febrile diseases and diseases of the joints, esophagus, heart, kidneys, nervous system and internal secretory glands are discussed. The book is beautifully illustrated and contains a mine of useful material. To the reviewer, however, it seems that differential diagnosis does not lend itself well to treatment as an independent subject; in fact, much of the matter given here is simply a duplication of what is found in general textbooks of medicine.

The Human Mind. By Karl A. Menninger. Second edition. Price, $5. Pp. 504. New York: Alfred A. Knopf, 1937.

Dr. Menninger has produced a solid yet readable book, and the profusion of brief case histories, graphically presented, will undoubtedly appeal to the lay reader. Just what, if any, purpose is served, however, by attempting to initiate the general public into the mysteries of psychiatry is another question. Had Pope lived today, he surely would have had this question in mind when he warned: "Drink deep, or taste not the Pierian spring." Every one knows that the newspaper reader promptly worries about having all the symptoms enumerated in the patent medicine advertisements; may not a similar and perhaps more serious disturbance result from reading popular psychiatry?

Tuberculose du tube digestif. By A. Cade, P. Santy and J. Heitz. Price, 80 francs. Pp. 410, with 27 illustrations. Paris: Gaston Doin & Cie, 1937.

This book is one of a series of monographs on tuberculosis published by the Bibliothéque de la tuberculose, founded by Chantemesse, Poncet and Collet. Tuberculosis of the gastrointestinal tract has been investigated intensively in recent years, and this volume constitutes a review of the laboratory and clinical development in this field. Theory is given due consideration, but particular attention is paid to treatment, including surgical procedures. An extensive bibliography adds greatly to the usefulness of this book.

Les hépatites. By Maurice Loeper, M.D. Price, 60 francs. Pp. 262, with 47 illustrations. Paris: Masson & Cie, 1937.

In this monograph the author deals systematically with various forms of hepatitis. There is much interesting material, but the classification of the various types does not seem entirely clear or satisfactory. However, the reports of cases make it possible for those accustomed to other classifications to follow fairly well the author's views. A considerable bibliography is included.

Allgemeine Elektrodiographie. By Prof. Dr. Eberhard Koch. Second edition. Price, 3 marks. Pp. 40, with 37 illustrations. Dresden: Theodor Steinkopff, 1937.

This little outline reduces to forty pages the essentials of electrocardiography with the aid of excellent charts and diagrams.